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THE USE OF DIBENAMINE AND NOREPINEPHRINE IN THE OPERATIVE TREATMENT OF PHEOCHROMOCYTOMA

Report of Two Cases*

GEORGE F. CAHILL, M.D.,† AND JAMES C. MONTEITH, M.D.‡

NEW YORK CITY

IN RECENT years the diagnosis of pheochromocytoma has been facilitated by the advent of several new agents. The use of intravenous pyelography, retrograde pyelography and perirenal air insufflation[1] has already been well established. The histamine test of Roth and Kvale[2] has proved of value in cases of paroxysmal hypertension due to pheochromocytoma. However, it must be remembered that cases of positive responses have been noted in which exploration revealed no pheochrome tumor.[3] The intravenous injection of tetraethyl ammonium bromide has been reported by LaDue and his co-workers[4] as producing a paroxysmal rise in blood pressure in pheochromocytoma. This test has an advantage not possessed by the histamine test in that the extent of the rise can be controlled by changing the position of the patient. Mecholyl is another agent first used by Guarneri and Evans[5] to produce a paroxysmal hypertension in a case of pheochromocytoma.

Perhaps the best agent developed to date to distinguish persistent hypertension due to pheochromocytoma is benzodioxane (piperidylmethylbenzodioxane or 933F) when used as described by Goldenberg and his co-workers.[6] Recently another adrenolytic agent has also been utilized in cases of pheochromocytoma. Dibenamine (dibenzylbetachlorethylamine hydrochloride) was demonstrated by Hecht and Anderson[7] to have an effect on the sympathetic nervous system in man. Spear and Griswold[8] and Hoch[9] utilized this drug in the therapy of a case of paroxysmal hypertension due to pheochromocytoma. The action of the drug is more prolonged than that of benzodioxane, lasting from twenty-four to seventy-two hours. One must be cautious of its side-effects during administration. The dose recommended is 5 to 7 mg. per kg. of body weight, given in an infusion of 300 to 500 cc. of saline solution. Caution must be observed in controlling the rate of flow; at least an hour should be taken for administration. On the basis of the prolonged adrenolytic action of this drug and of its beneficial effect on the well-being of the patient, we felt that it also could be beneficially used immediately prior to and during operation in these cases. Its prolonged depressor effect would facilitate the manipulation of the tumor during operation by blocking the marked rise in pressure that occurs on handling these tumors and that at times has resulted in death. In using such an agent we have, of course, eliminated a diagnostic aid: namely, the rise in pressure that occurs on manipulating pheochrome tissue.

Another adjunct in the therapy of pheochromocytoma has been added to our armamentarium to control fall in blood pressure after removal of the tumor. Holton[10] has recently demonstrated that pheochromocytomas contain significant amounts of norepinephrine, a compound differing only slightly in chemical composition from epinephrine. Goldenberg and his colleagues[11] have demonstrated a difference in the action of this drug and epinephrine on the cardiovascular system in man. They demonstrated that the intravenous infusion of epinephrine resulted in an increase in cardiac output but in a fall in peripheral resistance. Thus the pressor effect of epinephrine was believed to be due to the fact that the increased cardiac output outweighed the decrease in peripheral resistance because of the vasodilatation in the muscles.

Norepinephrine, on the other hand, when similarly infused exhibited little or no alteration of cardiac output, but there was a significant increase in overall peripheral resistance.

Epinephrine also was shown to have disturbing side-effects, namely, flushing, palpitations and cardiac arrhythmias. These findings were not noted with norepinephrine, the patient being unaware of a rise in pressure during infusion.

*From the Squier Urological Clinic, Columbia-Presbyterian Medical Center, New York. Made possible by the Albert K. and Mary Lasker Fund. The dibenamine hydrochloride used in this study was supplied by the Smith, Kline and French Laboratories.

†Professor of urology, College of Physicians and Surgeons, Columbia University, New York City; director, Department of Urology, Columbia-Presbyterian Medical Center.

‡Assistant resident in urology, Presbyterian Hospital, New York City.

Because of the difference in the actions of the two agents, it was believed that norepinephrine would be a better one to use during the operative and postoperative period in pheochromocytoma to control fall in blood pressure after removal of the tumor. The recommended dose is 4 mg. in 1000 cubic cm. of saline solution. The infusion is continued for twenty-four hours after operation, with the rate of flow being controlled by fluctuations in the blood pressure. Frequent blood-pressure readings are necessary.

Case Reports

Case 1. M.E., a 49-year-old woman, was admitted August 20, 1949, with the complaints of severe occipital headaches, blurring of vision, anorexia and vomiting. She also had

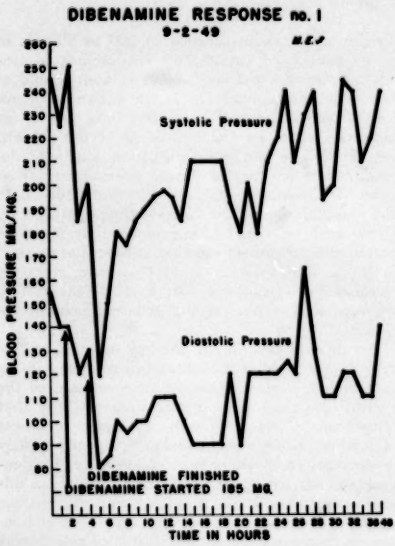

Figure 1.

Note the prolonged lowering of the blood pressure of approximately twenty-four hours' duration.

experienced attacks of profuse diaphoresis and palpitations, usually followed by extreme weakness. Her hypertension was first discovered in September, 1948, when she consulted an ophthalmologist because of blurring of vision. He referred her to an internist, who treated her as a case of hypertension, with salt-free diet, rice diet and potassium thiocyanate. A benzodioxane test was performed on her in September, 1949, and a suggestive fall in blood pressure was observed. She had suffered a rather marked weight loss because of persistent nausea and vomiting. Her hypertension had been persistent and her course had simulated that of malignant hypertension.

Physical examination disclosed an extremely emaciated woman, appearing much older than her stated age and weighing 77 pounds. There were multiple soft, flesh-colored papillomas over the entire body, some pedunculated and some with sessile bases. Fundi showed marked papilledema, hemorrhages and exudate. The neck veins were moderately distended. The lungs were clear, but the heart was enlarged to the left with a harsh precordial systolic murmur, normal sinus rhythm and a rate of 120. The abdomen revealed no masses or tenderness. The blood pressure was 240/130, the pulse 120 and the respirations 24.

On admission and during her hospital stay, blood count, blood urea nitrogen, blood sugar, preoperative and postoperative glucose tolerance tests, serum sodium and potassium, chloride solution, phosphorus and calcium were normal. Electrocardiograms showed increased amplitude of the R waves in Leads 2 and 3 and the character of the P waves suggested the possibility of auricular enlargement. Chest x-ray films showed generalized pulmonary emphysema. Prior to operation the basal metabolism was +38 per cent. An x-ray film of the abdomen showed a 1-cm. area of calcification overlying the midportion of the right kidney, which on intravenous pyelogram was shown apparently to occupy the infundibulum of the right lower calyx. Bilateral aerograms were unsuccessful because of failure of air to enter the right suprarenal area (due to adhesions) and because of superimposed gas on the left side. Urinalysis showed a ++++ albuminuria with occasional white blood cells on microscopical examination.

Because of her vomiting and anorexia, the patient was given daily infusions of 5 per cent dextrose in saline solution and 5 per cent dextrose in water. On August 24, 1949, a benzodioxane test was performed and was interpreted as a positive response. The test was repeated on August 30 and was again positive.

In order to observe the effect of a more prolonged lowering of the blood pressure, dibenamine, 6 mg. per kg. of body weight, was given on September 2, according to the method of Spear and Griswold (Fig. 1), and the blood pressure was recorded every hour for forty-eight hours. All but 45 cc. of a 500-cc. solution was injected. However, the injection was stopped because the patient complained of weakness of her right arm and leg; on physical examination she was noted to have paresthesias of the right side as well as weakness of the facial and tongue muscles. These symptoms, attributed to the sudden and relatively prolonged cerebral anoxia with the fall in blood pressure, gradually cleared and in several hours the patient was feeling much better and no longer exhibited the signs of hemiplegia. On the morning after the injection, the patient was able to take nourishment for the first time since entering the hospital three weeks previously. Five days later a repeat dibenamine test was performed, being started approximately thirty-six to forty hours prior to the expected time of operation (Fig. 2), so that the drug would be exerting some depressor effect in the operating room. The patient tolerated this test better than the first. The transient signs of hemiplegia, again on the right, were less marked and lasted only one to two hours. However, about twenty-six hours after injection, the patient had a bout of frank tetany, with carpopedal spasm and a positive Chvostek sign. These symptoms were partially relieved by calcium gluconate given intravenously. Serum sodium potassium, chloride concentration, carbon dioxide-content and calcium were not remarkable and after an infusion of 500 cc. of glucose in saline solution that afternoon and another on the morning of the operation, the patient felt better.

On the 20th hospital day the patient was operated on through a transverse upper-abdominal transperitoneal incision. At operation both kidneys appeared normal. The right adrenal gland was palpated as normal but could not be made out visually because of adhesions in the region of the gall bladder. The calculus previously mentioned was noted to lie within the gall bladder. Palpation along the aorta and in the pelvis revealed no evidence of tumor. The left kidney appeared normal, but a small amount of apparently normal left-adrenal tissue was observed to be compressed by a 5 by 3.6 by 2.8 cm. tumor mass. The blood vessels leading to the tumor were identified and ligated, with a resultant drop in blood pressure (Fig. 3). Noradrenaline was started at this point, with maintenance of a fairly stable blood pressure, as can also be seen in Figure 3. The operation was completed and the patient returned to the ward in good condition. The noradrenaline infusion was continued after the operation for twenty-four hours, being run very slowly, with its rate increased only if the blood pressure showed a ten-

dency to drop markedly, which it did not do in this case. One of the skin lesions was removed and on microscopical examination proved to be a neurofibroma, a lesion that has been noted in 20 per cent of our cases.

Grossly, the specimen was roughly ovoid in shape and weighed 55 gm. Assay of the tumor showed it to contain 14 per cent norepinephrine (1.4 mg. per gm. of tumor) and 86 per cent epinephrine (8.17 mg. per gm. of tumor). Microscopically, the picture was typical of a pheochromocytoma.

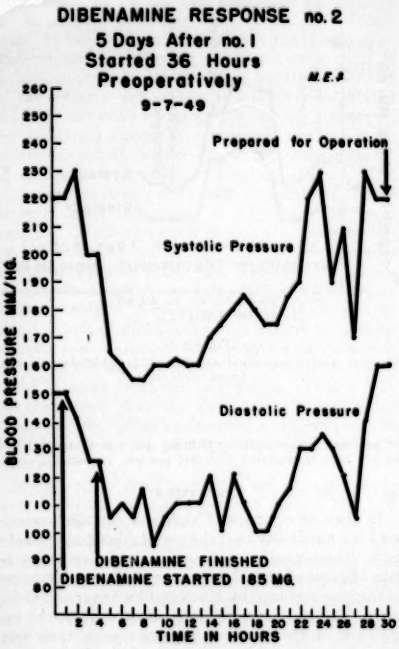

FIGURE 2. *Response to Dibenamine Five Days Later in the Same Patient.*

There were some areas of necrosis, and in some locations the cells were vacuolated. Along the margin of some of the sections were remnants of compressed normal adrenal tissue.

The patient's postoperative course was relatively uneventful. However, her blood pressure did not drop to within normal levels and on the day of discharge, the 22nd postoperative day, was 174/130. Her appetite was excellent; on discharge she had gained six pounds. A repeat benzodioxane test on her 17th postoperative day was normal, rendering unlikely the possibility of the presence of more pheochrome tissue. Her basal metabolic rate was only +18 per cent, as compared to + 38 per cent prior to operation. The glucose-tolerance test was roughly parallel to the preoperative levels, both being normal curves. A histamine test was not performed because of the patient's poor condition. She was discharged home on her 42nd hospital day.

CASE 2. H. B., a 41-year-old man, was admitted on September 16, 1949, with the complaint of recurrent attacks of dizziness, headaches, palpitation and sweating. He recalled that in 1938, while hammering nails, he had experienced a sudden attack of excruciating occipital headache, with throbbing, flushing, palpitations, trembling, weakness and sweating. The attack lasted about fifteen minutes and with its subsidence he felt extremely weak. He suffered a similar attack about two weeks later and thereafter continued to have three or four attacks monthly. However, during the ensuing ten to eleven years he had noted that the attacks had gradually become more frequent, until at admission he was having five to six such attacks a day, of five to ten minutes' duration. The severity of the symptoms was not so notable as in the beginning and he no longer had headaches, but he was suffering from nausea and occasional vomiting. At no time had he lost consciousness or experienced convulsions. Blood-pressure readings observed during attacks had ranged as high as 280/150 and after attacks as low as 80/50.

He was admitted to another hospital on June 20, 1949, with a history of a two-hour attack, more severe than usual, accompanied by dyspnea, precordial oppression and frothy hemoptysis. He was treated for a left-ventricular failure, but no digitalis was given. Diagnostic studies at the hospital showed a positive benzodioxane test, a mildly diabetic glucose-tolerance curve and the clinical observation of labile blood pressure. An exploratory laparotomy was performed through a right-subcostal incision, after forty-eight hours'

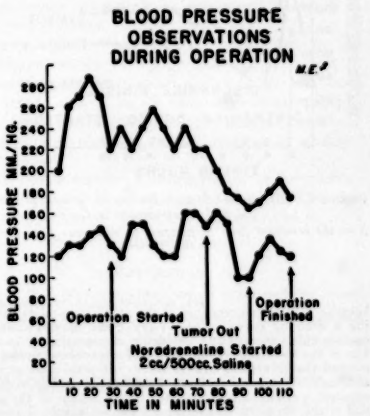

FIGURE 3.

Note that despite manipulation of the tumor the blood pressure did not tend to rise to extremely high levels. Norepinephrine was given to prevent a marked drop in pressure after removal of the tumor.

preoperative administration of dibenamine. The right adrenal gland was reported as normal and abdominal palpation, including the left adrenal area, revealed no significant findings. His postoperative course was uneventful, except that he continued to have attacks similar to his preoperative ones. He was then referred to this hospital for further evaluation and treatment.

Physical examination revealed a well developed, well nourished man. Examination of the fundi showed slight narrowing and tortuosity of arterioles but no exudate or papilledema. The lungs were clear, but the heart was

enlarged on percussion to the left anterior axillary line in the sixth intercostal space. It had a regular sinus rhythm and sounds of good quality. The aortic second sound was equal in intensity to the pulmonic second sound. The blood pressure was 100/80. The abdomen revealed a healed right subcostal and flank incision, no masses or tenderness and no palpable organs. A small varicocele was found on the left side. The remainder of the examination was normal.

Since he had been adequately studied by laboratory methods at the other hospital we did not believe that an extensive examination was necessary. On admission and during his hospital stay the blood count and blood urea nitrogen were normal. Urinalysis showed a ++++ albuminuria, no glycosuria and 5 to 12 red blood cells and 1 to 3 white blood cells per high-power field on microscopical examination. The blood sugar was elevated to 190 mg. per 100 cc. A glucose-tolerance test, however, was not done

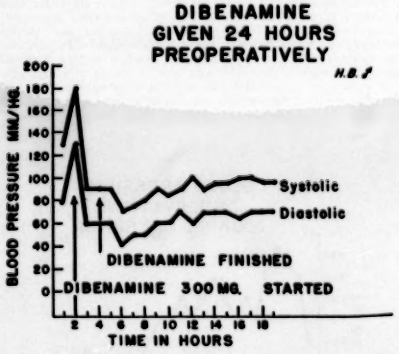

FIGURE 4. *Dibenamine Started During an Attack of Paroxysmal Hypertension in Case 2.*

Note the resultant drop in pressure to what was a normal level for this patient.

because it had been reported at the other hospital as exhibiting a diabetic curve. Chest x-ray films showed moderate cardiac enlargement but no evidence of congestion. An x-ray film of the abdomen was normal, and intravenous pyelograms showed the kidneys to excrete the dye in poor concentration, although no unusual findings were noted. A left aerogram outlined a rounded protuberance in the region of the upper end of the left psoas measuring 3.8 cm. in length. There was also a small rounded shadow 2.5 cm. in diameter in the region of the upper pole of the left kidney. The findings were interpreted as suggestive of pheochromocytoma.

Twenty-four hours prior to the operation the patient was given an infusion of glucose in saline solution containing 300 mg. of dibenamine (5 mg. per kg. of body weight), the effects of which are shown in Figure 4. On the 5th hospital day the left renal area was explored through a transverse flank incision and a 12-cm. round encapsulated pink tumor mass was removed from the area just medial to the pelvis of the left kidney, posterior to the renal vessels. Norepinephrine (2 cc. per 500 cc. of saline solution) was administered slowly throughout the operation and for thirty-six hours after operation to prevent rapid fall in blood pressure. Blood-pressure observations during operation are recorded in Figure 5. The patient's postoperative course was uneventful. The wound healed by primary intention and the patient was symptomatically improved. A histamine test showed no significant rise in blood pressure and was interpreted as negative, suggesting that the presence of excess secreting pheochrome tissue was unlikely. The patient was discharged on his 11th postoperative day.

Microscopically the tumor was characteristic of pheochromocytoma. Assay of this tumor revealed it to contain

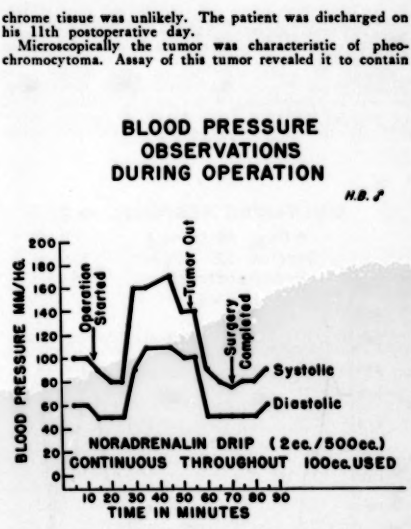

FIGURE 5.

Note less marked pressure rise than would be expected on manipulation of this tumor.

54 per cent norepinephrine (8.8 mg. per gm. of tumor) and 46 per cent epinephrine (7.5 mg. per gm. of tumor).

DISCUSSION

In their recent paper Cahill and Aranow[3] considered the possibility that the use of dibenamine might be a valuable adjunct in the preoperative preparation of cases of pheochromocytoma, in consideration of the case reported by Hoch and by Spear and Griswold. The two cases reported above confirm the experience of the previous reporters with their one case of paroxysmal hypertension. In both these new cases, one simulating a malignant hypertension persistent in character[12, 13] and the other a typical case of paroxysmal hypertension, dibenamine was given twenty-four to forty-eight hours prior to operation so that its effects would be evident at operation. In the case of persistent hypertension, two injections were given five days apart, with the patient showing improvement in the interval between the injections. As can be seen in Figure 3, the effect of the drug had almost been dissipated in regard to blood-pressure observations at the time of operation. In retrospect, it seems that it probably would have been better to operate when the pressure was lower.

A previous case reported by Cahill[14] showed a similar improvement due to a spontaneous throm-

bosis in the main artery to the tumor. This thrombosis occurred during a period of paroxysmal hypertension and was associated with a high fever and delirium. On abatement of the fever the tumor was removed surgically without any reaction at the time of the handling of the tumor. The tumor was found to be undergoing ischemic necrosis secondary to vascular thrombosis at removal, and the amount of hormone secreted or available for secretion was small. Hecht and Anderson[7] consider the effect of dibenamine to be on the muscle nerve endings in the smaller arterioles, that is, on the effector cells. It has been postulated that the dibenamine replaces the hypothetical substance sympathin E in combining with the mediator substance formed in the effector cell. Thus it has been suggested that an ineffective compound is formed. However, the inhibiting effects of sympathin would still be unaltered, which would explain the specification of dibenamine on certain excitatory effects of the adrenergic system. Both tumors removed in the present cases had areas of infarction and focal necrosis. The assumption is that the lessened volume of adrenalin-containing tissue produced smaller amounts of pressor substance. The pressure did not tend to rise to extremely high levels in the handling of the tumors in these cases. The question still remains whether dibenamine is a factor in causing necrosis and infarction. This could be due to anoxia in the tumor as a result of the prolonged fall in blood pressure produced by the drug. Thus it may be postulated that the drug exerts a secondary effect on the pheochromocytoma as well as its primary one on the effector cells of the vascular system.

Moreover, in both cases the use of norepinephrine[5, 6] during the operation and during the first twenty-four hours after operation prevented a marked drop in blood pressure without giving rise to the side-effects occasionally encountered with epinephrine. The effect of the norepinephrine was not so marked in Case 1 as in Case 2 because the blood pressure did not tend to approach hypotensive levels at any time but in fact remained elevated throughout the patient's hospital stay, although it was considerably lower than preoperative levels. In Case 2 the effect of norepinephrine was more noticeable because of the tendency of the blood pressure to drop to shock levels during the first two postoperative days.

The assay of the tumor in Case 1 showed it to contain 14 per cent norepinephrine, which, according to Goldenberg,[15] is the amount one would expect to encounter in the normal adrenal gland. In Case 2 the tumor contained 67 per cent norepinephrine. The percentage of norepinephrine generally found in pheochromocytomas has been from 50 to 90.

After operation both patients were tested to determine if all excess pheochrome tissue had been removed. In Case 1 a benzodioxane test was performed because the patient's blood pressure was still elevated, and it was felt that if a drop in the pressure did occur it would not be harmful. The test was negative, and it was assumed that the elevated pressure probably represented an essential hypertension. In Case 2 a histamine test was performed, rather than a benzodioxane test, because of the low level of the normal blood pressure throughout the hospital period. This test was also negative.

Summary

Two cases of pheochromocytoma have been presented, one with a sustained blood pressure simulating a malignant hypertension and the other exhibiting paroxysmal attacks of hypertension. Dibenamine was administered to both patients in the immediate preoperative period, so that the effect of the drug might be evident at operation. The effect of the drug during the handling of pheochromocytomas at operation has been discussed. The possibility that the drug had a secondary effect on the pheochromocytomas themselves in which necrosis and infarction were noted has also been suggested. This may have been the result of anoxia in the tumor secondary to prolonged lowering of the blood pressure.

Norepinephrine was used in both cases in the immediate postoperative period, and its effect in maintaining stable blood-pressure levels has been considered, as well as its advantage over epinephrine, because it increases peripheral resistance and does not increase cardiac output or produce arrhythmias.

The postoperative administration of benzodioxane or histamine to determine the absence of further excess pheochrome tissue was utilized, and in both cases the test used was negative.

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BACTERIUM ALCALIGENES (ALCALIGENES FAECALIS) INFECTIONS IN MAN*

LOUIS WEINSTEIN, M.D.,† AND EDWARD WASSERMAN, M.D.‡

BOSTON

BACTERIUM alcaligenes (Alcaligenes faecalis) is usually a harmless saprophyte in the human intestinal tract. On occasion, however, it may invade the tissues of man and produce a wide variety of clinical syndromes; this paper is concerned with an infection of this type that occurred in a patient who had infectious mononucleosis, and with a review of the literature on this subject.

Bact. alcaligenes is a gram-negative rod that shows considerable variation in cell size but is usually longer and thinner than *Escherichia coli*. It is motile and fails to ferment any of the common carbohydrates. Litmus milk is rendered strongly alkaline and a characteristic brown color is produced on potato.[1] The organism was first isolated by Petruschky[2] from stale beer in 1889 and again in 1896 from human feces, at which time it was first named *Bacterium alcaligenes faecalis*.

A number of cases of infection of man by this bacterium have been recorded, the clinical picture varying according to the tissue invaded. Thus localized disease such as meningitis, conjunctivitis and so forth, as well as more general syndromes confused with typhoid and rheumatic fevers, have been described in this connection. In some cases the organisms have been recovered from sites in which they probably did not produce the primary disturbance, as, for example, gallstones and renal calculi. The reports of the cases of this infection that have appeared in the literature are reviewed below and classified on the basis of the outstanding clinical manifestations that they presented.

Syndrome of rheumatic fever — bacteremia. Anderson[3] reported two patients who appeared at first to have severe rheumatic fever with valvular and myocardial lesions associated with painful swollen joints and who showed no response to salicylate therapy. Blood cultures in both revealed *Bact. alcaligenes faecalis*. Whether the recurrent arthritides and cardiac lesions were the direct result of invasion by the organisms from the intestinal tract over long periods of time or whether they represented instances of unrelated bacteremia in previously rheumatic subjects could not be ascertained.

Hepatitis. An instance of severe recurrent hepatitis in which cultures of the blood during the acute phase of the disease revealed *Bact. faecalis alcaligenes* in large numbers was recorded by McIntyre.[4] The patient was treated with an undenatured bacterial antigen prepared from the causative organism, with eradication of the bacteremia in forty-eight hours.

Enteric infections. A number of cases of enteric infections associated with *B. alcaligenes* have been reported. One case in which the clinical picture resembled that of a mild typhoid fever with uncomplicated recovery was described by Wyatt.[5] Headache, fever, chilly sensations and general malaise were present; fever persisted for fifty-seven days. Blood count and urinalysis were within normal limits. Four and nine days after the onset of symptoms, *Bact. alcaligenes faecalis* was isolated from the blood stream. Stool culture yielded this organism thirty-two days after the beginning of the illness. The serum agglutinin titer was 1:80 with the strain isolated from the feces. Serologic tests for *Salmonella typhi*, *Salmonella paratyphi* and *S. schottmülleri* were consistently negative. Ravenel[6] observed a patient who died on the sixth day of illness and in whom autopsy revealed an anatomic picture consistent with typhoid fever, and *Bact. alcaligenes* in the spleen and intestinal ulcers. Among the significant findings were marked splenomegaly, slight hepatomegaly and congested mesenteric lymph nodes. In the lower ileum were a number of small ulcers between which the lymphoid tissue was hypertrophied. Solitary lymphoid follicles in the colon were markedly enlarged and some revealed early ulcers with slightly elevated edges and yellow centers.

A large number of cases of enteric disease observed by Shearman and Moorhead[7] in Egypt during World War I showed bacteremia due to *Bact. alcaligenes*. Stool and other examinations revealed the same organisms and the absence of any other pathogenic enteric bacteria. Agglutinin titers as high as 1:200 were found in many of the patients, whereas serums from control cases were negative. The onset of the illness was sudden and characterized by chills, headache, occasional nausea and vomiting and generalized aching. Abdominal pain and constipation were noted frequently, relative bradycardia was the rule and hepatomegaly and splenomegaly were absent. White blood-cell counts averaged 8800, with normal differentials, and urine examinations revealed no abnormalities. The authors stressed the importance of the bacteriologic findings in establishing the diagnosis. They offered the interesting suggestion that in more temperate climates *Bact. alcaligenes* is a harmless intestinal saprophyte but in the tropics, where gastrointestinal disturbances are frequent, the "catarrhal"

*From the Haynes Memorial and Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine.

†Associate professor of medicine, Boston University School of Medicine; lecturer in infectious diseases, Harvard Medical School; chief, Department of Infectious Diseases (Haynes Memorial), Massachusetts Memorial Hospitals.

‡Formerly, assistant resident in medicine (Haynes Memorial), Massachusetts Memorial Hospitals; resident in medicine, Fifth and Sixth (Boston University) Medical Services, Boston City Hospital.

condition of the bowel provides a *locus minor resistantiae*, and the formerly harmless organism becomes invasive and produces bacteremia. Hirst[8] suggested that although *Bact. alcaligenes* is essentially only weakly virulent it may become pathogenic for man when there is underlying disease of the intestine. This organism was isolated by Hirst from the stools, urine and blood of patients who had sudden onset of high fever, a "toxic" appearance and ill defined complaints.

Webster[9] reported 11 nursing infants with severe diarrhea and grossly bloody stools in three of whom cultures of the sagittal sinus and external jugular vein revealed *Bact. alcaligenes*; one child died. The mechanism of infection by this organism was considered to be the same as that proposed by Hirst.[8]

Gall-bladder, renal-tract, eye, lymph-node and appendiceal infections. Various types of localized infection, with and without bacteremia, may be produced by *Bact. alcaligenes*; these are illustrated by the following reports from the literature. Daniel and Greene[10] recorded a case of recurrent attacks of gall-bladder colic in which the stones removed at operation contained *Bact. alcaligenes*. This organism was found in renal calculi by Stuart and others.[11] Their patient had recurrent symptoms of renal lithiasis for a number of years; during one episode *Bact. alcaligenes* was isolated from the urine. Nephrotomy performed shortly after this attack revealed calcium-carbonate and calcium-phosphate calculi, from the interior of which *Bact. alcaligenes* was recovered. Blood culture was negative but the serum, in a dilution of 1:200, agglutinated this organism. Administration of autogenous vaccine was thought to have accelerated wound healing and convalescence. *Bact. alcaligenes* was thought by MacKenzie and Ratner[12] to have been the etiologic agent in a case of bilateral pyelonephritis with septicemia; the bacillus was recovered from blood, urine and feces.

Smith and Fraser[13] and Popoff and Spanswick[14] observed 1 case each of renal-tract infection with *Bact. alcaligenes* occurring during pregnancy. The micro-organism was recovered repeatedly from feces, urine and blood and from the uterus in Smith and Fraser's patient; bacteremia was absent in the other.

Weiss[15] demonstrated *Bact.-alcaligenes* bacteremia in 3 patients with gangrenous appendicitis. Blood cultures in 50 other patients with normal appendices or chronic appendicitis were sterile. A case of cervical abscess in which the etiologic agent was *Bact. alcaligenes* was recorded by Pohl and Raymond.[16] Barrow[17] described an epidemic of conjunctivitis due to this organism occurring on a British naval vessel.

Meningitis. Only 8 cases of infection of the meninges by *Bact. alcaligenes* are reported in the literature. Gatewood's[18] patient developed Jacksonian epilepsy due to a traumatic brain cyst following skull fracture. Operation resulted in the development of meningitis, and *Bact. alcaligenes* was recovered from the cerebrospinal fluid; uneventful recovery occurred after lumbar puncture. In another instance of meningeal disease due to this organism, described by Mason,[19] the source of the infection appeared to be a spontaneous opening in a meningocele. Spray and Hawk[20] observed a patient who, after bilateral otitis media, developed meningitis from which *Bact. alcaligenes* was isolated. In Goldberg's[21] case of meningitis the mode of entry appeared to be direct contamination of blood and spinal fluid by rectal discharges. A patient who for four months had bacteremia, meningeal infection and polyarthritis due to *Bact. alcaligenes* and who finally recovered after treatment with sulfadiazine was recorded by Voorhies and Wilen.[22] *Bact. alcaligenes* was isolated in pure culture on four occasions from the spinal fluid and once from the blood stream in a case studied by Terry and his co-workers.[23] No preceding infection or portal of entry could be detected. Recovery followed treatment with streptomycin and sulfadiazine. The first two cases of *Bact.-alcaligenes* bacteremia and meningitis in the newborn infant were reported by Bischoff and his co-workers[24]; no focus of infection was demonstrable.

Bacteremia without evident local focus. Hazen and Mortillaro[25] described a 49-year-old woman with sudden onset of chills, "septic" temperature, extreme prostration and abdominal distention. The white blood-cell count was 13,500, with 91 per cent neutrophils. The diagnoses considered initially were typhoid or undulant fever and some type of bacteremia. Agglutinins for *Salmonella typhi*, brucella, and *Pasteurella tularense* could not be demonstrated in the third and fourth weeks of the disease and enteric pathogens were not isolated. *Bact. alcaligenes* was isolated in pure culture from the blood one week prior to death. Weintraub and Neter[26] reported a case of bacteremia with *Bact. alcaligenes* complicating diabetes mellitus. The bloodstream infection was self-limited and disappeared without treatment. Andrieu and others[27] also noted an instance of bacteremia with this organism.

Case Report

A young woman with furunculosis of the auditory canal developed fever and shaking chills after incision and drainage of this lesion. Study in the hospital revealed infectious mononucleosis and bacteremia with *Bact. alcaligenes*. A complicating fusospirochetal angina responded to penicillin therapy. The bacteremia cleared apparently spontaneously. The active role of *Bact. alcaligenes* was established by the development of a rising antibody titer; the heterophil agglutinin was proved to be identical with that present in infectious mononucleosis by the Davidsohn exclusion test.

E. M., a 27-year-old woman, was admitted to the Haynes Memorial Hospital with a chief complaint of fever of eleven days' duration. Two weeks prior to admission she had noted a dry, scratchy sensation in the pharynx, more marked on the right side, which disappeared shortly after the local application of argyrol. Two days later, after taking a hot shower, the patient felt weak and was unable to move her limbs in

normal fashion. She remained in bed, but on the following day felt improved and visited friends in the evening. During this visit she developed low-back pain, became hot and "felt sore all over and couldn't move." Her temperature was 100° orally, and she returned to bed. During the next few days a severe frontal headache was present. Four days prior to admission a furuncle of the right auditory canal was first noted; this was incised by a physician, after which full doses of sulfadiazine were administered. The following day the local abscess was drained again and penicillin was instilled into the canal. The sulfonamide was discontinued because of anorexia and a "burning" sensation in the pharynx. Thereafter the temperature rose daily to between 102° and 104°F. and the patient experienced three severe shaking chills.

Physical examination on admission to the hospital revealed a well developed, well nourished woman in no acute distress. The temperature was 102° rectally, the pulse 108 and the respiratory rate 20. The blood pressure was 100/60. The tonsillar lymph nodes were enlarged and tender, and there were smaller palpable nodes in the posterior cervical triangles. Both tympanic membranes appeared thickened, dry and dull. Landmarks were distinguished with difficulty and the light reflexes were much diminished. On the midportion of the posterior wall of the right auditory canal was a small moist furuncle, from which exuded a small amount of serum. The remainder of the physical examination was within normal limits, except for a Grade I precordial systolic murmur, which was loudest at the base.

The white blood-cell count on admission was 6900, with 24 per cent neutrophils, 25 per cent small lymphocytes, 48 per cent large atypical lymphocytes, 2 per cent large mononuclear cells and 1 per cent basophils. The "atypical" lymphocytes had the features of those usually associated with infectious mononucleosis. The hemoglobin was 12.3 gm. per 100 cc. and the sedimentation rate was 33 mm. in one hour. A Schick test was positive and a tuberculin patch test negative. Urinalysis was within normal limits. A blood Hinton test was negative. The heterophil antibody titer was 1:1280 on admission and rose, within a week, to 1:2560. Agglutinins for brucella and enteric pathogens were not significantly elevated. Electrocardiogram was normal and x-ray examination of the chest disclosed only enlarged right hilar nodes. Repeated cultures from the nose, throat and furuncle of the ear revealed only alpha-hemolytic streptococci, hemolytic *Staphylococcus aureus*, nonhemolytic *Staph. albus* and diphtheroids. On one occasion beta-hemolytic streptococci were isolated from the pharynx. Blood cultures on the first, second and third days in the hospital yielded organisms that were identified as *Bact. alcaligenes*.

For the first six days, the temperature rose daily to 103°–104°F. (rectally), although the patient had no complaints other than weakness and excessive perspiration. On the sixth day, penicillin (20,000 units every three hours given intramuscularly) was started because of the persistent fever and because of moderately severe fusospirochetosis of the pharynx, as revealed by numerous ulcers covered by gray pseudomembrane that showed a marked predominance of *Fusiformis fusiformis* and spirochetes. The lesions in the upper respiratory tract subsided rapidly and the temperature declined to normal in ninety-six hours. This was accompanied by symptomatic improvement and disappearance of weakness. Blood cultures made after the third hospital day were sterile. The patient was discharged, fully recovered, sixteen days after admission.

Bacteriologic and Serologic Studies

The organism isolated from the patient's blood was studied by various bacteriologic methods in order to determine its identity. It was a moderate-sized, somewhat plump gram-negative rod that exhibited sluggish motility. It grew readily on tryptose-yeast-heart infusion agar, with or without added blood, and produced no hemolysis. The colonies were about the same size as those of *E. coli* and had a spreading, undulate edge. No indole was formed. Litmus milk was turned strongly alkaline and a dark-brown pigment was produced in potato slants. Dextrose, levulose, lactose, maltose, sucrose, xylose, mannitol, sorbitol, dulcitol and inositol were not fermented. These findings identified the organism as *Bact. alcaligenes* or *Alcaligenes faecalis*.

Studies of the development of antibodies to *Bact. alcaligenes* were carried out at periodic intervals, using as antigen the strain isolated from the patient's blood. At the time of admission to the hospital the agglutinin titer of the serum was 1:32; ten days later it had risen to 1:128. The final examination was carried out approximately four weeks after onset of the bacteremia; at that time the patient's serum agglutinated her own strain of *Bact. alcaligenes* in a dilution of 1:512. The low agglutinin content at the beginning of the illness, followed by the rise to fairly high level during the convalescent period, confirmed the causal relationship of *Bact. alcaligenes* to the disease in this case.

Infections other than infectious mononucleosis are known occasionally to produce increase in heterophil agglutinins for sheep cells in the serums of man and animals. Meningococcic meningitis, gonococcal septicemia, scarlet fever, rubeola, tuberculosis, filariasis, pasteurellosis, pneumonia and bacteremia due to *E. coli* are among the diseases in which such elevations have been recorded. The literature on this subject is reviewed by Bornstein.[28] Because of the possibility that the high titer of heterophil agglutinin in our patient might have been due to the presence of *Bact. alcaligenes* and not to infectious mononucleosis, her serum was examined on two occasions by the Davidsohn exclusion test.[29] These studies revealed that the antibody was not absorbed by ground guinea-pig kidney but was almost completely removed by contact with boiled-beef erythrocytes. These findings, together with the demonstration of "atypical" lymphocytes, confirmed the diagnosis of infectious mononucleosis.

Summary and Discussion

A patient who had infectious mononucleosis with an intercurrent bacteremia due to *Bact. alcaligenes* has been described. The focus from which the organism entered the blood stream was most likely a furuncle of the external auditory canal, which was twice incised and drained. Bacteriologic studies of this lesion were not carried out prior to admission to the hospital, and careful cultural examination did not disclose this organism after hospitalization. The diagnosis of infectious mononucleosis appears to be on firm ground on the basis of the demonstration of characteristic "atypical" lymphocytes and a high serum level of heterophil agglutinin, which was absorbed by boiled-beef erythrocytes but not by guinea-pig kidney. Determination of agglutinating antibody for the strain of *Bact. alcaligenes* isolated from the patient's blood with a rise in titer established the causal relation between this

organism and the bacteremia and ruled out inadvertent contamination of the blood cultures. Recovery from the bacteremia occurred apparently spontaneously, since cultures of the blood had become negative prior to the administration of chemotherapy. Although the patient received penicillin this was given only because of the appearance of a moderately severe fusospirochetal pharyngitis.

This case demonstrates clearly that organisms that are essentially "nonvirulent" may produce disease in man under certain circumstances. Usually such infections occur when there is a local or generalized decrease in the resistance of tissues to invasion. In the patient described in this paper, the decrease in neutrophilic leukocytes may have been very prominent, as it frequently is during the course of infectious mononucleosis, and probably accounted for loss of local defense against penetration by bacteria, resulting in the development of bacteremia. In the light of this case and of others that we have had an opportunity to study,[30] it is evident that any organism found circulating in the blood stream should not be totally disregarded and dismissed as simply a "contaminant." Every effort should be made to evaluate the causal relation of such findings to the disease process by appropriate studies, which should include at least the determination of an immune response.

Conclusions

A case of infectious mononucleosis in which *Bact. alcaligenes* was isolated from the blood stream is described.

A review of the literature reveals that this organism may produce bacteremia, meningitis, hepatitis, renal and biliary-tract infections, acute enteritis, infections of the eye, lymph nodes or vermiform appendix and syndromes resembling rheumatic or typhoid fever.

Attention is called to the importance of so-called "nonvirulent" organisms in the production of human disease under circumstances in which localized or generalized decrease in defense mechanisms occurs.

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ACUTE BENIGN PERICARDITIS*

MORTON G. BROWN, M.D.†

FRAMINGHAM, MASSACHUSETTS

PERICARDITIS not associated with tuberculosis, rheumatic fever or other expected causes was the subject of a study by Barnes and Burchell[1] in 1942. Certain features of this disorder, such as the rapid changes in heart size,[2] the difficulty in differential diagnosis from acute coronary occlusion,[3] the specificity of the electrocardiographic pattern,[4] and the lack of complications,[5, 6] have been commented on in subsequent reports. Few data concerning the subsequent courses of these patients have been recorded.

During the past four years 13 patients with acute pericarditis have been studied at this hospital. Case reports concerning 7 of these patients illustrating the main features of this disorder were selected. Data obtained from the remaining 6 patients are included in the tabulation and the discussion.

CASE REPORTS

CASE 1. P.C. (C.V.A.H. 5838), a 28-year-old truck driver, was admitted to the hospital because of severe precordial pain and shortness of breath of five hours' duration. This pain was made worse by deep inspiration.

The temperature was 100°F., the pulse 110, the respirations 24 and the blood pressure 105/60. There was a loud pericardial friction rub heard at the third left intercostal space. The remainder of the physical examination was negative.

The white blood-cell count was 14,500. X-ray examination of the chest revealed a normal heart size and clear lungs. The electrocardiogram showed elevated ST intervals in Leads 1, 2 and 3 and diphasic T waves in chest leads V_1 through V_6.

The precordial pain, dyspnea and fever gradually subsided over a period of ten days. The friction rub persisted for five days. The electrocardiographic changes persisted for three weeks. After discharge he returned to work. He has been asymptomatic and has continued to show completely normal findings during the following three years.

CASE 2. L. L. (C.V.A.H. 6587), a 36-year-old steamfitter, had suffered from a sore throat for five days, for which he was given sulfadiazine. Ten days later he developed oppression in the chest, cough, shortness of breath and fever. Because of the persistence of symptoms he was admitted to the hospital.

The temperature was 100° F, the pulse 120, the respirations 18 and the blood pressure 120/76. The heart was enlarged to percussion, with a loud pericardial friction rub heard all over the precordium. There was impaired resonance and somewhat diminished breath sounds at the right base.

The white blood-cell count was 13,700. X-ray examination of the chest showed a markedly enlarged heart, which did not return to normal size until one month later. The lungs were clear. The electrocardiogram showed elevation of the ST intervals and inverted T waves in all limb leads and chest leads V_4, V_5 and V_6. These changes persisted for five weeks.

He ran a febrile course for four weeks. The pericardial friction rub lasted three weeks. After discharge he returned to work, and when last seen three years later was asymptomatic and was completely normal at examination.

CASE 3. C. D. (C.V.A.H. 20723), a 51-year-old bartender, had noted fatigue and shortness of breath for two weeks. For one week he noted a dull aching pain in the left lower anterior chest, made worse by lying on the left side. These symptoms gradually increased and he was referred to the hospital.

The temperature was 102.6°F., the pulse 90, the respirations 22 and the blood pressure 104/72. The heart was slightly enlarged to percussion and a loud pericardial friction rub was heard all over the precordium. A pleural friction rub was heard over the right lower lateral and posterior chest.

The white blood-cell count was 17,800. X-ray examination of the chest showed moderate enlargement of the heart. There was pleural thickening and an indication of small amounts of fluid in the costophrenic sinuses bilaterally. The electrocardiogram revealed elevated ST intervals and inverted T waves in Leads 1, 2 and 3 and chest leads V_2, V_4, V_5 and V_6.

The pericardial friction rub lasted four days. The patient ran a febrile course for six days. Twelve days after admission x-ray revealed a normal-sized heart and clear lung fields. The electrocardiogram was entirely normal four weeks later.

Two years later a Grade III epidermoid carcinoma of the larynx was removed without event. Three years from the onset of his pericarditis he had a completely normal examination.

CASE 4. D. B. (C.V.A.H. 17643), a 32-year-old sheet-metal worker, two weeks prior to admission developed precordial pain that radiated across the lower anterior chest and was constant but made worse by change in position and deep respiration. He continued to work until he developed shortness of breath and palpitation.

The temperature was 101.6°F., the pulse 80, the respirations 18 and the blood pressure 100/68. The heart was markedly enlarged to percussion and there was a moderately loud pericardial friction rub over the midprecordium. There was dullness and diminished breath sounds at the left lung base.

The white blood-cell count was 14,000. X-ray examination of the chest showed moderate enlargement of the heart, a triangular plate-like density of the lower left lobe and some pleural thickening over the posterior portion of the right lower lobe. The electrocardiogram showed elevation of the ST intervals and inverted T waves in Leads 1 and 2 and chest leads V_2, V_4, V_5 and V_6.

He ran a febrile course for two weeks, during which time the precordial pain and pericardial rub persisted. He was given aureomycin, 250 mg. every two hours, for four days without any alteration of the course. Ten days after admission the heart size was reported as normal on x-ray examination. Clearing of the lungs took two months. His electrocardiogram returned to normal in eight weeks.

One and a half years later he was free of symptoms and had an entirely normal examination.

CASE 5. C. K. (C.V.A.H. 17632), a 40-year-old woodworker, four months prior to admission developed substernal pain in the region of the second and third intercostal spaces on the left. This was made worse by inspiration and change of position. X-ray films of the chest at this time was reported as negative.

He remained well until seventeen days before admission, when he suffered a recurrence of the substernal pain. A temperature of 102°F. was recorded, and he was given 6 capsules of aureomycin. The dose is uncertain. He continued to have pain and was admitted to the hospital.

The temperature was 102°F., the pulse 100, the respirations 22 and the blood pressure 126/84. The heart was moderately enlarged. A moderately loud pericardial friction rub was heard just to the left of the sternum in the fourth

*From the Medical Service, Cushing Veterans Administration Hospital, Framingham, Massachusetts.
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†Instructor in medicine, Harvard Medical School; assistant chief of medicine, Cushing Veterans Administration Hospital.

and fifth intercostal spaces. Numerous fine crackling rales were heard in the midaxillary line on the left.

The white blood-cell count was 11,600. X-ray examination of the chest showed moderate enlargement of the heart. There was a triangular area of density in the left costophrenic sinus and some plate-like atelectatic changes in the right lung base. The electrocardiogram showed inverted T waves in Leads 2 and 3 and chest leads V_1, V_2, V_3 and V_4.

During the first five days he was quite ill, continued to have fever, substernal pain and pericardial friction and on one day showed paroxysmal auricular flutter. On the sixth hospital day he was started on aureomycin, 0.75 gm. every six hours. Within twenty-four hours his temperature returned to normal, his friction disappeared and he became asymptomatic.

The enlarged cardiac shadow and abnormal lung findings persisted for eight days. The electrocardiogram returned to normal in two months.

One and a half years later examination was entirely negative. He was doing physically demanding work without symptoms.

Case 6. A. L. (C.V.A.H. 10640), a 25-year-old student, nine months prior to admission, had an attack of anterior chest pain, lasting five or six days, for which he did not seek medical attention. Two weeks before admission he developed an upper-respiratory infection. One week later he experienced sharp pain beneath the lower portion of the sternum, made worse by inspiration and change in position. He developed fever, was admitted to the college infirmary and in a few days was transferred to Cushing Veterans Administration Hospital.

The temperature was 102°F., the pulse 60, the respirations 20 and the blood pressure 100/70. The heart was moderately enlarged. A pericardial friction rub was heard to the left of the sternum in the third and fourth intercostal spaces. The lungs were clear.

The white blood-cell count was 16,500. X-ray examination showed the heart to be moderately enlarged, and there was an area of consolidation, with some pleural fluid in the posterior portion of the left costophrenic sinus. The electrocardiogram showed elevation of ST intervals and inverted T waves in all limb and chest leads.

He appeared to be very ill. His febrile course lasted six weeks. A pericardial friction rub could be heard during the first three weeks. The increased heart size and the changes in the lungs lasted three weeks. The electrocardiogram did not return to normal for three months. He finally was well enough to return to school.

Six months from the onset of the illness he was readmitted because of recurrence of substernal and left parasternal pain of six days' duration.

The temperature was 100°F. The heart was not enlarged. No friction rub could be heard. X-ray examination of the chest was normal. The electrocardiogram showed flattening of T waves in the limb leads, which persisted for one week.

He became afebrile and asymptomatic within a few days, and has remained in good health during the subsequent two and a half years. His last examination was entirely negative.

Case 7. S. L. (C. V.A.H. 6989), a 36-year-old shipper, was first admitted to Cushing Veterans Administration Hospital with complaints referable to an old shell-fragment wound of the chest and shoulder. Physical examination, electrocardiogram and x-ray films were normal.

Two months later he was readmitted because of dull, aching substernal pain of four days' duration, made worse by change in position.

The temperature was 101°F., the pulse 120, the respirations 15 and the blood pressure 120/75. The heart was enlarged. The remainder of the physical examination was normal except for the scars of his old injury.

The white blood-cell count was 12,000. X-ray examination showed the heart to be considerably enlarged. The electrocardiogram showed elevation of ST intervals in Leads 2 and 3, and lowering of T waves in Leads 1, V_5 and V_6.

On the fourth day of illness a pericardial friction rub was heard. This persisted for two days. He became afebrile and asymptomatic on the sixth day. The enlargement of the heart lasted eight days, and the electrocardiogram returned to normal in two weeks. He was discharged in good health.

Five weeks after the onset he was readmitted for recurrence of sharp, steady precordial pain. The temperature and white-cell count were again elevated. X-ray examination again showed enlargement of the cardiac shadow, which persisted for eleven days. The electrocardiogram now showed ST elevations and T-wave inversions in all limb leads and in Leads V_4, V_5 and V_6.

These changes lasted for two months, although he was afebrile and asymptomatic after two weeks.

He has remained well and at work during the succeeding three years. The x-ray films are shown in Figure 2.

Discussion

During the past four years 13 patients with acute benign pericarditis have been studied. Their ages

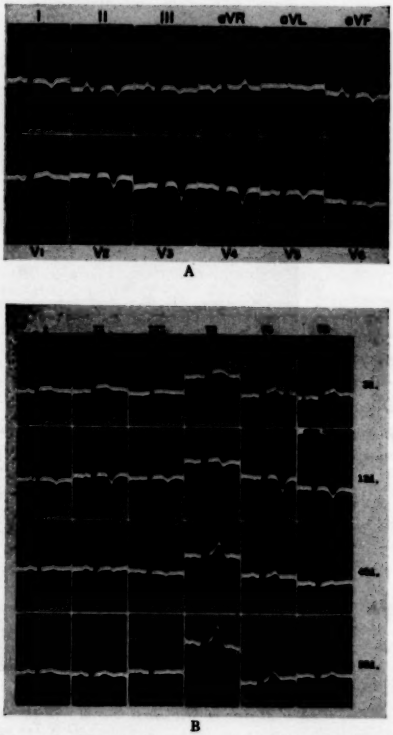

Figure 1. *Electrocardiogram in Acute Benign Pericarditis.*
A = *Twelve-lead tracing showing ST–T changes in most leads.*
B = *Evolution and regression of pattern.*

ranged from 21 to 53 years, with 3 over 50. Each gave a history of substernal or precordial pain lasting hours to days. In most instances this distress was made worse by a change in position, but in some patients it had all the characteristics of that

described in myocardial infarction. Many patients had associated fatigue, cough, dyspnea or antecedent respiratory infection.

In 10 of the 13 patients a pericardial friction rub was heard. The 3 lacking this sign were not observed during the early days of their illness. The friction rub usually made its appearance during the first days of the illness and lasted from hours in the mildly ill to weeks in the severely ill. Eight of the 13 patients exhibited increased cardiac dullness to percussion. Six had dullness to percussion, rales or altered breath sounds at the lung bases. Two had signs consistent with fluid at the lung bases. The pericardial friction rub and the cardiac enlargement were the outstanding physical findings.

All the patients showed fever ranging from 100 to 103° F. and leukocytosis varying between 11,000 and 18,000. Cold agglutinins were not found in serums from 5 patients so tested. Electrocardiographic changes were present in every case. These ranged from elevated ST intervals and inverted T waves in all limb and chest leads to similar changes restricted to a few leads (Fig. 1). One showed a transitory paroxysmal auricular flutter. None showed prolongation of the PR interval. The usual electrocardiographic signs of myocardial in-

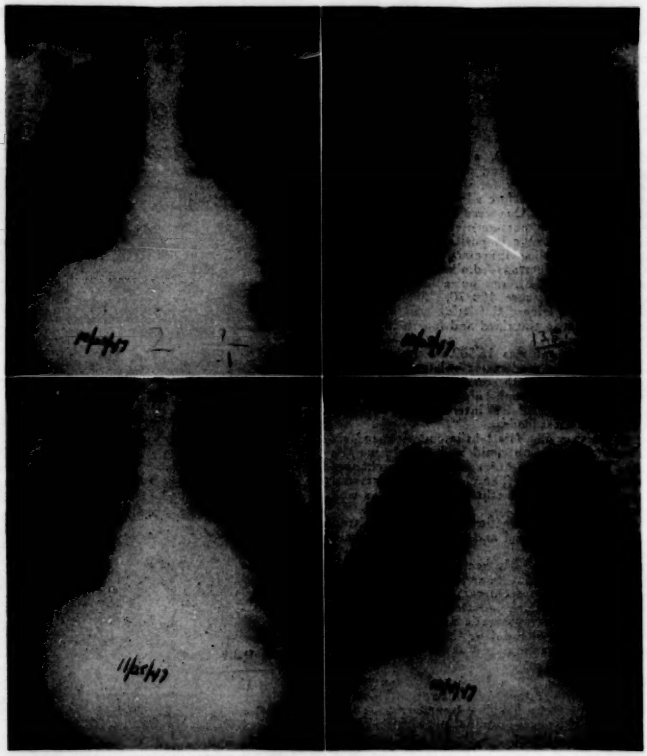

FIGURE 2. *X-ray Films of Chest in Case 7.*
A = *At time of first admission.* B = *Eight days later.* C = *At time of recurrence five weeks later.* D = *Ten days after recurrence.*

farction, such as abnormal Q waves in limb or precordial leads, disappearance of R waves in precordial leads, intraventricular conduction defects or other alteration of QRS complex, were not observed in any case. The electrocardiogram remained abnormal for from two weeks to three months.

Pulmonary changes seen in the x-ray films of 6 patients were variously interpreted as pleural effusion, atelectasis or pneumonia. Two patients had moderate bilateral pleural effusion. The degree of cardiac enlargement seen on x-ray examination could be correlated with the severity of the clinical course (Fig. 2). This enlargement persisted for one week to two months. The marked and rather rapid changes in heart size on x-ray examination were noteworthy. Wolff, in 1943, considered the various reasons for this change in heart size and concluded that acute cardiac dilatation rather than pericardial effusion was the most satisfactory explanation.[2] Inasmuch as no attempt at pericardial tap was made in any of these cases, no further evidence can be added.

None of the patients exhibited any evidence of myocardial or endocardial lesions or of disturbed function. None developed any manifestation of rheumatic fever or tuberculosis. None have shown any evidence to indicate constricting scars of the pericardium. Two patients had a recurrence of the illness one month and six months after the initial onset. All recovered. Penicillin was given to 4 without benefit. Aureomycin was given to 2. In 1 it may have affected the source of the disease (Case 5). In view of a recent report, aureomycin deserves further trial.[7]

Each of the 13 patients has been carefully observed for at least eighteen months, and 6 have been observed for more than three years. All are asymptomatic and have returned to their former employment. Each has a normal heart as seen on physical examination. No murmurs have appeared. Cardiac shadows are normal by x-ray examination. All electrocardiograms are normal. The outstanding diagnostic criteria are summarized in Table 1.

Summary

Thirteen patients with acute benign pericarditis have been studied.

The outstanding diagnostic criteria are pain in the chest, pericardial friction, characteristic electrocardiographic changes, rapid changes in heart-shadow size and a benign course.

Table 1. *Diagnostic Criteria (13 Patients).*

	No.	Duration
Precordial pain	13	Hours to days
Pericardial friction	10	Hours to weeks
Electrocardiographic changes	13	2–12 weeks
Enlarged cardiac shadow	8	1–8 weeks
Benign course and complete recovery	13	

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DISSEMINATED HERPES SIMPLEX (KAPOSI'S VARICELLIFORM ERUPTION) AND THE FAILURE OF PENICILLIN AND AUREOMYCIN TO INFLUENCE ITS COURSE*

MINERVA S. BUERK, M.D.,† AND HARVEY BLANK, M.D.‡

PHILADELPHIA

KAPOSI'S varicelliform eruption is now known to be a clinical syndrome characterized by a virus infection superimposed on a chronic dermatitis, usually an atopic eczema. The responsible virus is either the herpes-simplex virus or the vaccinia virus. When the etiologic agent is known, the disease is more aptly called "disseminated herpes simplex" or "generalized vaccinia."

In the past, these two virus infections of the skin could usually be differentiated only by specialized laboratory procedures, or by the microscopical demonstration in biopsies of early vesicles of the inclusion bodies characteristic of herpes simplex (Lipschütz bodies) or of vaccinia (Guarnieri bodies).[1, 2, 3] Tzanck has proposed a technic for demonstrating the "virus-type" giant cells in smears prepared from the base of vesicles that makes it possible to establish the diagnosis of herpes simplex with ease. A recent study by Blank and others has confirmed the accuracy and simplicity of this procedure, which is feasible in any medical laboratory.[4] Its practical value is indicated in the case presented in this paper.

Shortly after Wong and Cox demonstrated that aureomycin was effective in virus infections caused by the lymphogranuloma-psittacosis group of agents,[5] it was tested in herpes-simplex infections. The first preliminary clinical reports suggested a favorable response.[6, 7] Review of the cases reported, however, does not reveal sufficient laboratory studies to prove the diagnosis of herpes simplex or to establish the antibody titer for the virus of herpes simplex in the patient's serum at the onset of infection. In our experience, disseminated herpes simplex (Kaposi's varicelliform eruption) can occur as either a "primary" infection in a patient with no antibodies at the onset or as a "recurrent" infection in patients with a high titer of herpes-simplex antibodies. Although the so-called "recurrent" infections begin as an acute febrile illness indistinguishable from the "primary" type, their course is milder and of shorter duration. In such cases the temperature may subside in forty-eight to seventy-two hours, and the skin lesions heal promptly. Without adequate serum-antibody studies it would be difficult to differentiate the effects of the natural variable course of the disease and the effects of aureomycin.

A detailed study of the effect of aureomycin on herpes-simplex infections in chick embryos by Baldridge and Blank[8] failed to show any protective effect of the drug under controlled laboratory conditions. In the light of additional experience, which has demonstrated that aureomycin has no specific effect against any virus except the unusually large viruses of the psittacosis-lymphogranuloma group, it seems most unlikely that the drug would influence herpes-simplex infections.

The following case is reported because it demonstrates the several points discussed above.

CASE REPORT

R. M., a 27-year-old man, was admitted to the University Hospital on February 28, 1950, because of fever and a contact dermatitis of the face and neck superimposed on an atopic eczema. He had had recurrent flare-ups of atopic eczematous dermatitis since the age of three months, and petit-mal epilepsy since the age of nine years. One week before admission he developed an acute contact dermatitis from a coal-tar ointment. This dermatitis seemed to be subsiding, but at the time of admission he was acutely ill, out of proportion to the extent of the dermatitis, and he was admitted for study.

On admission the temperature was 103°F., the pulse 144 and the blood pressure 90/60. The face and neck were moderately erythematous, with numerous papules and excoriations topped by dried serosanguineous crusts. Oozing and fissuring were evident behind the ears and in the folds of the neck. A few scattered pustules were present on the forehead with moderate periorbital and perioral edema. The antecubital and popliteal spaces and the dorsum of the left foot were lichenified. There was moderate lymphadenopathy of the cervical, submental and submaxillary nodes. The conjunctival vessels were moderately injected. The gingivae were hypertrophied (dilantin). The lungs were clear; examination of the heart revealed a soft systolic murmur over the entire precordium. The remainder of the examination was noncontributory.

Laboratory examination revealed a hemoglobin of 115 gm., with a red-cell count of 5,000,000 and a white-cell count of 12,900, with 74 per cent neutrophils, 12 per cent monocytes and 14 per cent lymphocytes. Several atypical lymphocytes and heavy granulations of the neutrophils were observed. Urinalysis was normal except for a faint trace of albumin. The blood urea nitrogen and blood-sugar levels were normal. Serologic tests for syphilis were negative. The serum protein concentration was 8.3, with concentrations of albumin of 3.3 and of globulin of 5. The carbon-dioxide combining power was 66 and the serum chlorides 93 milliequiv. Culture of the pustules yielded alpha-hemolytic *Staphylococcus aureus* and alpha-hemolytic and beta-hemolytic streptococcus. The cerebrospinal fluid had 2 cells per cu. mm., with a protein content of 24 mg. and a sugar concentration of 87 mg. per 100 cc., and a chloride concentration of 140 milliequiv. per liter. Culture and smear of the fluid were negative for bacteria.

Course. By the evening of the admission date, there was frank oozing of the entire face and neck. The patient's fever rose to 105.4°F. rectally and he became more toxic. The following morning the neck and face were covered with multiple discrete vesicles, of which some had coalesced and others were umbilicated and pustular (Fig. 1 and 2). The patient was moribund and had multiple petit-mal seizures on the slightest stimulation. Nausea, vomiting, chills and pain in the head and neck were concomitant symptoms. The

*From the Department of Dermatology, University of Pennsylvania. Aided by a grant from the U. S. Public Health Service (RG 2388).

†Formerly, instructor in dermatology, University of Pennsylvania.

‡Assistant professor of dermatology, University of Pennsylvania; dermatologist, Children's Hospital, Philadelphia.

first virus studies were performed at this time and confirmed the diagnosis of disseminated herpes simplex. Throughout the following eight days the patient remained in a semicomatose condition but could be aroused sufficiently for oral medications. Fresh crops of vesicles continued to appear on the arms, hands and face on the 6th, 8th and 10th days. Subsequently the lesions gradually dried and involuted.

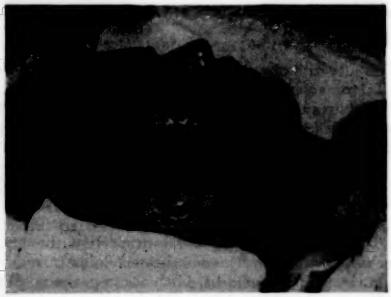

FIGURE 1. *Face and Neck of Patient, Twenty-Four Hours after Onset of Disseminated Herpes-Simplex Infection.*

There are discrete pustules on the ears, nose and neck, with confluent oozing lesions elsewhere.

By the 19th day only residual erythema and lichenification remained.

Therapy (See Fig. 2). The patient's dehydration and alkalosis on admission were treated with intravenous dextrose and saline solution. The intravenously administered fluids were continued daily and were supplemented by a minimum of 1000 cc. of protein hydrolysate (60 gm.) daily until the

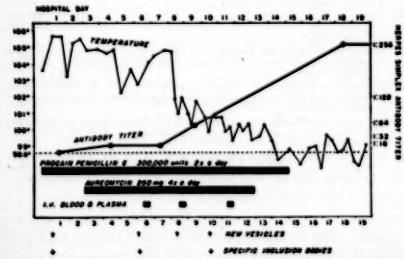

FIGURE 2. *Chart of Patient's Hospital Course, Including Medications and Herpes-Simplex Antibody Levels.*

patient was able to ingest adequate amounts of fluid. To this were added plasma and blood transfusions. The epileptiform seizures at the onset of infection were readily controlled with dilantin and phenobarbital.

On admission to the hospital the patient was given procaine penicillin G, 300,000 units twice daily, for fourteen days. On the second hospital day administration of aureomycin, 250 mg. four times a day, was started and continued for ten days. Local therapy consisted of continuous wet dressings on the affected areas during the acute exudative phase. A bland hydrophilic ointment was alternated with the wet dressings after crusting had occurred.

LABORATORY VIRUS STUDIES

The diagnosis of a disseminated herpes-simplex infection was proved in several ways. It was immediately established by demonstrating characteristic "virus-type" giant cells in smears prepared from the base of the vesicles according to the method of Tzanck.[4] Figures 3 and 4 illustrate several of these unique cells as seen with the Giemsa stain. Such cells are seen only in herpes simplex, herpes zoster and varicella. In the light of the clinical picture,

FIGURE 3. *Smear of Base of Vesicle, Air Dried and Stained with Giemsa Stain.*

Multinucleate epithelial giant cells containing two or more nuclei are numerous (x90).

however, herpes simplex was the only possible diagnosis. Additional studies were performed to make certain of this fact.

Biopsies of early vesicles were taken at the time of the preparation of cytologic smears. These showed the typical histologic picture, with both small eosinophilic and large basophilic intranuclear inclusions[1, 2, 9] in the epithelial cells, as well as the "virus-type" epithelial giant cells.

At the time the first smears and biopsies were performed, sterile swabs were taken of the vesicle fluid for virus culture. The swabs were rinsed in sterile saline solution containing 0.5 per cent gelatin, 500 units of penicillin and 100 units of streptomycin per cc. and inoculated onto the chorioallantois of ten-day-old chick embryos.[10] Typical herpes-simplex plaques were seen on the membranes, and the virus was passed serially three times to other eggs. Microscopical demonstration of typical inclusion bodies in the plaques proved them to be caused by the herpes-simplex virus.[9] No virus was

isolated from the spinal fluid in several passages on chick chorioallantoic membrane.

Serums were drawn periodically, and the titer of specific herpes-simplex neutralizing antibodies was determined against a known established strain (W) of herpes simplex.[11] The rise in titer, as indicated in Figure 2, establishes the patient's disease as a primary infection with the herpes-simplex virus.

FIGURE 4. *Higher Power of Another Field of the Preparation Seen in Figure 3 (x 285).*

DISCUSSION

It is apparent from inspection of Figure 2 that the patient's fever and acute illness continued for five days after the administration of aureomycin. In addition, new vesicles continued to appear and specific inclusion bodies were present in microscopical preparations as late as eight days after the first administration of the drug. As penicillin is known to have no effect on the virus of herpes simplex, it was used to control any secondary bacterial infection. If such bacterial infection were a prominent part of the clinical picture, its control with aureomycin might mislead the observer into believing that the aureomycin was acting against the virus infection. The failure of aureomycin to show even any nonspecific effect in this disease can possibly be attributed to the concomitant use of penicillin. The patient's course was essentially that of all the other patients we have observed with primary disseminated herpes simplex.

SUMMARY AND CONCLUSIONS

A case of herpes-simplex infection (Kaposi's varicelliform eruption) is presented.

The value of the rapid diagnosis of herpes-simplex infections by the cytologic-smear technic of Tzanck is indicated.

Aureomycin had no effect on this proved herpes-simplex infection. This is in accordance with earlier laboratory studies and refutes other preliminary clinical reports in the literature.

The importance of general supportive therapy, including parenterally administered fluids to maintain the fluid and acid-base balance in patients with this severe infection, is stressed.

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FIFTY YEARS OF MEDICAL PROGRESS

MEDICINE AS A SOCIAL INSTRUMENT: MEDICAL EDUCATION IN THE TWENTIETH CENTURY

C. Sidney Burwell, M.D.*

BOSTON

MEDICAL education has altered extensively in the fifty years from 1900 to 1950. This is partly because of the rapidity and extent of change in medicine itself and in general science, partly because of changes in the social and economic background of medicine and partly because of changes in the general field of education.

It is necessary to impose certain limitations on a discussion of this length; what is written here will be restricted to the history of medical education in this country during the period under discussion. Except for incidental reference, it will be necessary to ignore the great and, in some instances, catastrophic changes in European medicine. No mention, for example, will be made of the decline and fall of German medicine, of the developments of medical education in Russia or of the impact of war and social reorganization on British medicine. Nothing can be said of the extraordinary history of the introduction of Western medicine into Asiatic countries, particularly China, nor of the changes in the oldest American universities — those of our neighbors in Central and South America. These matters are not foreign to this discussion. The decline in the quality of medical education in many European countries in the last twenty years has increased the responsibilities of medical schools elsewhere. However, this discussion will be concerned only with medical education in the continental United States during the years 1901 to 1950.

Medical education, as has been said, exists in a social and economic framework. These fifty years have seen great changes in that framework. Growing population, expanding industry and wealth, participation in two great wars and many other influences have played their parts in altering the problems of medical education and the methods of meeting these problems.

The period from 1900 to 1950 has also been one of continuous and active interest in medical education as such. A perusal of Volume 142 of the *Boston Medical and Surgical Journal*, published in 1900, reveals an intense and articulate interest in the problems of medical education. This volume contains a classic article by Walter Bradford Cannon, then a student in the Harvard Medical School, entitled "The Case Method of Teaching Systematic Medicine." It could have been written yesterday. He speaks sadly of the "crowded curriculum." He discusses the case method as a teaching procedure and compares it with didactic lectures. In his spirited defense of the application of the case system to medical teaching he gives the following admirable summary of a useful principle that still animates, and should continue to animate, medical-school teaching in the clinic and the laboratory: "It is the particular patient, the concrete instance, that gives body and form to textbook abstractions, holds the attention, and stimulates the reasoning power." In this volume there was an editorial on the Annual Report of Harvard University. It called attention to the encouraging fact that 43 per cent of the medical students in the Harvard Medical School were college graduates. It stated eloquently that the Medical School departments needed more space, that new funds were needed for both Medical and Dental Schools and that there was an opportunity for a forward step in establishing closer relations between medicine and dentistry. The editor remarked: "The general ferment now going on is sure to result in marked improvement."

Dr. W. W. Keen, speaking as president of the American Medical Association in Atlantic City in June of 1900, was deeply concerned lest medicine, which he considered a worthy recipient, should obtain less than its fair share of total benefactions. He was especially concerned because he had counted 171 endowed chairs of theology in this country and only 5 endowed chairs of medicine. He looked forward hopefully to an increasing endowment for the support of professorships, laboratories and postgraduate training in medical schools, and he took particular interest in pointing out the great importance of scholarships and research fellowships.

References to the importance of postgraduate study are many and are strikingly similar, both in idea and phraseology, to many of the discussions of today. Let me quote from an address by Dr. Frederick C. Shattuck, given at Washington University, St. Louis, on April 26, 1900: "In conclusion, gentlemen of the graduating class, may I venture on one word of advice. You have been undergraduate students, you are about to enter on a lifelong period of postgraduate study. Remember that you are, every one of you, debtors to the Medical School, debtors even in the lower and pecuniary sense of the term, in that the fees you

*Research professor of clinical medicine, Harvard Medical School; physician, Peter Bent Brigham Hospital; visiting physician, Boston Lying-in Hospital.

have paid for your instruction do not nearly represent its cost."

Medical education is like the human body in that every part is functionally related to the whole, but it will be convenient to consider these closely interrelated matters under a series of separate headings.

Some Quantitative Aspects of Medical Education

The quantitative aspects of medical education, as well as many other essential matters, are well covered in the reviews of medical education that have appeared annually in the *Journal of the American Medical Association* during the half-century.

In 1901, according to the first educational number of the *Journal of the American Medical Association*,[1] there were 159 medical schools in existence. Registered in these 159 schools were 26,417 students. Of these, 5444 received their M.D. degrees that year. They were divided among four types of schools as follows:

"Regular" medical colleges	4879 graduates
"Homeopathic" medical colleges	387 graduates
"Eclectic" medical colleges	148 graduates
"Physio-medical" and nondescript	30 graduates
Total	5444 graduates

In 1950 there were in the United States 79 *approved* schools, including seven schools of the basic medical sciences whose work was limited to the first two years of the medical course. Of these 79 schools, fully a quarter were established *during the fifty-year period* under discussion, and many of the others have been reorganized during this same period. This means that about a hundred medical schools ceased to exist during our half-century period.

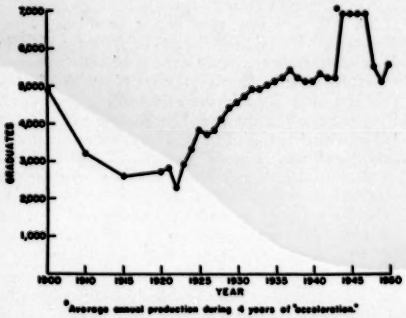

Figure 1.

In 1950 these 79 approved schools registered 25,103 students and awarded the M.D. degree to 5553 men and women. The striking similarity in the number of graduates during these two years a half century apart is sometimes taken as suggesting that medical schools have not increased their production of physicians during this period. Such a conclusion is quite against the historical evidence if that is regarded as a whole. Between 1906 and 1924 the number of medical schools in active operation fell from 162 to 79. During this period the annual number of graduates was also cut in half. It went from a high figure of 5747 in 1904, to a low point of 2304 in 1922. Thus one can say that at present the number of graduates is more than twice the number approximately of thirty years ago. Some of this material is shown graphically in Figure 1. Extra classes were graduated during the period of 1944 to 1947, and the number of graduates during this time is charted as the annual average.

A more up-to-date indication than any of these is the *first-year* enrollment of 1950-1951, the impressive figure of 7187.

What is represented, therefore, in the first part of Figure 1 is what Dr. Henry S. Pritchett of the Carnegie Foundation described in 1910 as "an enormous overproduction of uneducated and ill-trained medical practitioners." This overproduction, he points out, was not planned in the interest of the population at large but was the result of the operation of a large number of proprietary schools. The leading schools in 1900 (Johns Hopkins was an outstanding example) did a fine job by any standard; many others did not. Strong forces within and without the profession were operating to improve matters. It is not necessary to do more than mention the Council on Medical Education, the Association of American Medical Colleges, the famous "Flexner report"[2] of 1910, the stimulating generosity of great foundations and the leadership of universities. These and other forces led to a rapid diminution in the number of medical schools, to the improvement of those that remained and to the organization of new ones on an improving basis.

It is necessary now to consider briefly the adequacy of the present number of graduates. The significant figure in this matter is not the number of graduates but the number of doctors in relation to the total need. The number of graduates per year is one of the factors in the equation; another is the rate at which doctors are removed from practice by death or retirement. The falling death rate has played a role here, and a study of the figures in the annual educational number of the *Journal of the American Medical Association* will show that even during the years when the number of annual graduates was changing very little the number of physicians was increasing faster than

the population. In a recent article Dr. Willard C. Rappleye, dean of the College of Physicians and Surgeons of Columbia University, observes that between July 1, 1937, and June 30, 1942, the number of medical graduates from schools in the United States totaled 25,818. During the same five-year period, the deaths of 18,898 doctors were reported, leaving a net increment of physicians of 6920 for this five-year period. During the five-year period between July 1, 1942, and June 30, 1947, during part of which medical schools were on so-called "accelerated" programs, a total of 32,877 doctors were graduated and 16,435 deaths were recorded, leaving a net increase of 16,442. When the "increment" is over 1000 per year the number of physicians is increasing as fast as the population. During recent years, as may be seen, it is much higher than this. However, even with these gratifying increases, it is necessary for many reasons to increase further the production of physicians. This need becomes obvious in the light (if it can be called light) of the emergency that exists now and presumably will continue to exist for a period of years. Increase in the production of physicians is being brought about by the expansion of existing schools, by the conversion of two-year into four-year schools and by the creation of entirely new schools. All are expensive, the last especially so. It is necessary to move cautiously in this matter with due regard for the maintenance of standards, for the economical use of teaching personnel, of which there is a critical shortage, and with understanding of the interrelations of medical schools and community hospital services.

A word must be said about the estimation of need. There is no reason to believe that the number of physicians now required for a given number of people has any direct relation to the number that was required for the same number of people fifty years ago. Too many things have happened. Medicine has become infinitely more complex, and there are many more kinds of activities that require the participation of physicians. Public health is an example. On the other hand, during this same period there has been an enormous development of supplementary medical personnel — nurses, technicians, secretarial workers, librarians and all the host of people who *expand the capacity of a given number of doctors to do the total job of the profession.* There is urgent need, as medical education becomes longer and longer, more and more complex and more and more expensive, to make a more economical use of medical manpower. This is true all along the line: in community medical service, in hospitals, in medical schools, in Army, Navy, Air Force, Public Health Service and Veterans Administration. This is the first intelligent move in meeting a shortage.

Academic Medicine and the "Full-Time" Principle

In 1900 most of the teaching in medical schools was done by volunteer, unsalaried practitioners who generously gave their time and energy for the instruction of the next generation of physicians. As medicine and medical teaching changed and became more complex, it was increasingly evident that there was need for a group of men who were specially trained and who could devote all or almost all their time and energy to the university obligations of teaching and research. Historically and naturally, most of the early full-time workers in medical schools were in preclinical departments — anatomists, pharmacologists, physiologists, biochemists and bacteriologists. The development of full-time teachers, which in these fields involved both physicians and experts who were not physicians, proceeded gradually and without great controversy, but the situation was otherwise when the needs of teaching and research in departments related directly to the care of the patient began to require the full-time devotion of increasing numbers of men. Indeed, one of the most interesting controversies in medical educational circles during this half century has been the discussion of the so-called "full-time" system. Discussion of this usually bogs down in matters of definition of what is meant by the full-time system and of how the principle should be applied. I have never been much bothered by these technical matters of definition, but have been deeply concerned with application of the *principle.* Two things seem axiomatic to me. One is that the provision of opportunity for teachers and investigators to devote their time to teaching and investigation has been one of the major factors in the transformation of medical education in America during the past fifty years. The second is that full-time teachers not engaged in active practice cannot by themselves impart to students an adequate interpretation of the problems of medicine. They need, and will continue to need, the understanding, the participation and the collaboration of their part-time colleagues who are actively in practice in the community.

Let us give a little more consideration to the statement that the full-time principle is essential. Teaching is a difficult assignment. It requires time, learning, resourcefulness and the expenditure of energy. All the same things can be said of research. If teaching and research are the primary objectives of a medical school, as they should be, then it is necessary to have people on the staff with time to devote to these fundamental and primary objectives. This problem may be solved in a variety of ways; in other words, there is more than one road to salvation, just as there is more than one way to skin a cat, but all the ways to attain success in medical teaching and research demand the pro-

vision of time as well as opportunity for the person concerned. Through various types of organization, the full-time principle has been introduced more and more into medicine, to the great gain of medical education and research, to the benefit of medical students and to the benefit of hospital patients.

As the full-time principle was more widely applied there was, however, a simultaneous growth of influences that tended to cut down its effectiveness. One of these was the sad depreciation in the value of the dollar. When a medical school by great effort accumulates an endowment that permits it to pay full-time salaries to teachers, it is soon thereafter found that these salaries are no longer adequate. Then the teachers, in order to live at an acceptable level, find it necessary to supplement their salaries by time-consuming outside activities, such as practice, in volume not contributory to their academic accomplishment. Another influence tending to interfere with the teaching and research of academic personnel in medical schools is the growth of administrative complexity in school and hospital. This makes serious inroads on the time of the very persons who need to be free. Many phenomena contribute to it, including hand-to-mouth financing by annual grants, overexpanded departments, inadequate numbers of nonmedical administrative assistants and lack of clarity in university-hospital relations. Here is an opportunity to make a better and more economical use of medical manpower. Even with these and other problems, the "full-time" system (in the broad sense in which we are using the term) is an accepted and indispensable part of the organization of medical education.

Medical Schools and Universities

The full-time principle was not the only fundamental principle of organization that contributed to the stature and stability of medical education during this half-century. Another factor was the change in the organizational basis of medical education during these fifty years. Some schools grew up around a hospital, following a pattern familiar in England, where there are many "hospital schools." Others were established in some sort of relation to a parent university. Even so, in 1900 either a great many medical schools were entirely independent of university control or the university control was a matter of formality rather than of organic connection. As I look at the history of medical education in this country in fifty years, I am impressed by the growing importance of university influence in the evolution of many of the most productive medical schools. Medical education, with all its implied associated duties, is too important to be left to any single profession or to a faculty made up of any homogeneous group. It needs the broadening effect of connections with fundamental scientific departments and with university officials concerned with and experienced in the organization of educational enterprise, and it needs all the other tremendous services that universities can give to medical education. One of the dangers faced by medical education is that it may become technologic training. When it does that, it will become preparation for last year's medicine instead of for the medicine of twenty years hence; it will be less and less productive in terms of research, and it will not be good enough. A close and responsible relation to a university is the best protection against this type of arteriosclerotic decline.

Universities can play another important role in relation to medical schools. They tend to be long-lived institutions, outlasting administrations, governments and even nations. They tend to be relatively free institutions and may be able to assist medical schools to remain free from the domination of hampering influences, whether these be licensing bodies, specialty boards, professional societies or the Federal Government.

A "Principle" of Teaching

One of the important trends in the method of teaching and the point of view of teachers has been a tendency toward what we may call rationalism in teaching. Teachers have attempted during this half-century to encourage the student to acquire an understanding of the phenomena of medicine, rather than simply a remembered knowledge of them. The development of this method of teaching is due partly to the recent advances in the knowledge of disease, partly to the presence of well-trained teachers devoting their lives to academic careers and partly to the influence of professional teachers in other fields. In the writer's opinion, this change in the methodology of teaching is so important that it may be one of the major contributions of this period to medicine. It is certainly one of this period's chief contributions to medical teaching. This is a radical statement and requires defense. *Effective* performance in as complicated a field as medicine is not accomplished by rule of thumb but demands an *understanding* of the multiple factors, internal and external, that produce, accelerate, retard or abolish disease processes. That is one reason; there is another. Formidable changes take place with prodigious rapidity in the field of medicine. No one can practice the medicine he was taught in medical school for more than a very short period after his graduation. It is those physicians who have some understanding of the biologic processes involved in health and disease who are most capable of adjusting themselves and their medical work to these changes.

There is a growing recognition of the importance of this general concept. Recognition of its importance is one of the reasons for the impressive growth in our knowledge of what is curiously called "path-

ological physiology" and for the great amount of time spent by teachers of medicine and surgery in the elucidation of physiologic mechanisms. Recognition of the importance of this concept is also a reason for insisting on progress in the matter of bringing together and interrelating the teaching of the so-called preclinical subjects and that of medicine and surgery. It has become clear that the understanding of the problems of patients is necessarily dependent on an understanding of physiology, pathology, biochemistry and other preclinical sciences. To relate effectively the teaching in these two fields is a challenging and difficult problem for teachers in all departments. This change in attitude and method also serves to emphasize an important fact that must be remembered by those concerned with the organization and operation of medical schools. This fact is that, in a school that aims at giving its students a proper understanding of disease, it is not possible to separate teaching from research, or to separate either from the care of patients. They are inseparable, these three; to recognize and utilize this fact is a source of strength.

We may now turn our attention to a brief consideration of some of the major functions that together make up the job of medical education.

Candidates for the Degree of Doctor of Medicine

Certainly the first objective of medical schools is to provide their candidates for the M.D. degree with educational opportunity. A variety of changes have taken place in the pattern of undergraduate medical education during the last fifty years.

The requirements for admission are considerably different, so that medical students as a group start at levels of knowledge and of maturity quite unlike those of 1900. Most students in medical schools today are graduates of colleges, and nearly all have had at least two years of college. They come to the medical schools equipped with at least the beginnings of chemistry, physics and biology. What is needed in addition is a better foundation of "general education." General education has always been important for physicians and is now indispensable for effective performance. Detailed entrance requirements were not described in the first educational number of the *Journal of the American Medical Association*, but in 1910, when there were 133 medical schools in existence, no fewer than 99 of them announced their readiness to accept applicants on the basis of four years of high school or less, and only 27 schools were demanding as much as two or three years of college as a prerequisite to medical study.

There has been an increase in the number of applicants for admission to medical schools, so that in recent years there have been many more applicants than there are places in the schools. It is to be expected that such a situation would lead to an improvement in the caliber of medical students. In general, it appears that such an improvement has occurred, but it is limited by two important factors: First, although methods of selection have improved, they are still far from perfect, and second, some schools, especially some state universities, practice geographical restriction to such a degree that they are not able to accept the most competent applicants for admission.

Women in medicine have grown in both distinction and number. (In 1904 there were 1109 women medical students, or 4.3 per cent of the total. In 1950 there were 1806, or 7.2 per cent of the total.) All but three schools admit them, but their opportunities for hospital training are fewer than for men, as is postgraduate opportunity all along the line. This is probably a reason that many capable and interested women by-pass medicine for careers in related fields of science.

Once a student is in school today, he finds a good many differences from what his predecessors found fifty years ago. On the average, he finds much better facilities for teaching in terms of laboratory facilities, hospital facilities and teaching personnel. The content of the curriculum and the methods of instruction have also changed to some degree, although not so much as is justified by the changes in medicine. Some general directions of change may be mentioned. Certain new subjects have been added. Instruction in preventive medicine, public health, psychiatry and social and environmental factors are examples of this kind of curricular amendment. More important than the addition of new categories has been the transformation of the subject matter in all departments. Every department has shared in this transformation. Because this new wine has been placed in old departmental bottles, it is quite impossible to judge the change in the subject matter of the curriculum by the study of medical-school catalogues.

Methods of teaching have altered quite as much as the subjects considered in teaching. A great change in the approach to medical education in the past fifty years has been the development of student participation and student responsibility. This has been achieved through development of teaching in laboratories and hospitals, where the student is responsible not only for planning many aspects of his own education, especially his reading and methods of study, but also for actually acquiring facts and points of view through laboratory experiments and through the study and observation of individual patients. This change in medical education has been a gradual one and is unevenly distributed between medical schools and between departments in medical schools. Enough experience has been had to indicate clearly that the principle of student participation and responsibility is good in terms of what students know and are able to do at the time of graduation and in terms of their own capacity

to continue their own educations after the end of the period of formal schooling.

There also has been, as has been suggested before, an admirable, although far too gradual, progress toward an appropriate interrelation of the subject matter in clinical and preclinical courses.

One thing that has *not* been done to an adequate degree is the removal from the curriculum of subjects and points of view that are less important than they were fifty years ago. The evolution of the curriculum has been largely through additions to it. When the medical course reached the length of four years and the curriculum was filled to bursting the expansion was transferred to the postgraduate years, and most medical students now continue the study of medicine for a period of years after their graduation from medical school. It is not necessary to include in the undergraduate curriculum certain matters that were essential in 1900, because men will have an opportunity to acquire knowledge of these during their years of hospital training. This will be referred to later. It is mentioned now in order to point out that this fact has been and will continue to be reflected in the evolution of the undergraduate curriculum. As medical education becomes longer and longer and more and more costly, the obligation to establish an economical curriculum becomes more obvious.

Candidates for the Degree of Doctor of Philosophy in One of the Medical Sciences

In 1900 almost all the teachers in medical schools were physicians, including the teachers in the preclinical departments. One of the changes occurring during this half-century has been an increasing need, as medicine changes and as medical sciences advance, for professionals in the various fields of medical sciences. Medical education requires a large number of teachers and investigators in physiology, anatomy, biochemistry, pharmacology, pathology and bacteriology, and one of the factors interfering with the expansion of the capacity of medical schools is the shortage of adequately trained teachers and investigators in these fields. This is perhaps the most acute shortage in the personnel of medical education. The shortage is created by many factors, including the ever-widening demand for experts in these subjects. This demand comes not only from evolving medical schools but also from other university departments, from hospitals, from research institutes, from government departments and from industry.

It is interesting to note that although all these types of organizations are consumers of well trained teachers and investigators in these fields, the medical school is the organization that is generally asked to spend its substance and time in their training. There is no doubt that medical schools have a large share of responsibility for the basic training of these indispensable workers, but it is hardly just to ask them to expand this part of their program unless some new mechanism is found for financing it.

In this area of the provision of instruction leading to the degree of Doctor of Philosophy in one of the medical sciences is to be found another example of the basic dependence of medical schools on membership in a university. It is hardly possible, for example, to supply adequate training in these fields without the assistance of departments of chemistry, physics, biology and mathematics. Moreover, it is highly desirable for the future of both medicine and biochemistry (for example) for the M.D. and the Ph.D. candidates to work side by side with mutual understanding and stimulation.

The Advancement of Knowledge by Research

One of the most impressive alterations in institutions for medical education during the past fifty years is the explosive expansion of formal research activities. This has had profound effects on the content and method of medical teaching, on the training and character of those who enter the field of medical education and on the point of view and activities of students. The juxtaposition of research and teaching has proved advantageous to both. It has also introduced a great number of organizational and financial problems.

There are many advantages in the association of research and teaching. Teaching in departments in which research is going forward is likely to be alive, to change progressively and to be relatively up-to-date. The research of individual workers is enriched by their contact with teaching, and teaching obligations tend to make well rounded investigators. One of the great advantages of a medical school in a university as a site for research is the possibility of having in a single institution a wide spectrum of research in a general field. This spectrum in a university with a medical school can run all the way from theoretical physics to the sick child in a hospital. Knowledge and illumination can flow in both directions along the line of this spectrum. Advances in physiology and biochemistry have been taken over by physicians working with patients and expanded into new knowledge of disease. The current also sets in the other direction. Observations made by men working with patients, such as that of the effect of liver in pernicious anemia, have in their turn fertilized and reactivated areas of preclinical and fundamental science.

Advanced Training for Practice, Teaching and Research

One of the outstanding phenomena of the past fifty years has been the expansion of so-called graduate teaching in medicine. This expansion has been gradual. Early in this half century the "intern year" became increasingly popular; now almost all medical graduates have at least a year's internship, and 29 medical licensing boards require such a

year of hospital experience as a prerequisite to licensure. Residencies and assistant residencies have steadily increased in number, and fellowships have offered increasing opportunity for training in research and teaching.

In the early part of our period there was an agreeable and effective flexibility in postgraduate training. Men with academic ambitions or who sought specific specialty training went here and there and built up an experience tailored to their own objectives, as nearly as they could. From time to time farsighted men spent some years in biochemistry, pathology, physiology or bacteriology as part of their preparation for careers in medicine or surgery.

These simple and individualistic days appear to have vanished, and postgraduate training has been to a greater extent formalized and systematized. The American Board of Ophthalmology was founded in 1916; the American Board of Otolaryngology in 1924, and the American Board of Obstetrics and Gynaecology in 1930. Other groups fell rapidly into line, and now, at the end of the fifty-year period, there are *19* such "approved examining boards in medical specialties."

The chief functions of such boards are said to be: "(a) to conduct investigations and examinations to determine the competence of voluntary candidates for certificates issued by the respective boards, (b) to grant and issue certificates of qualification to candidates successful in demonstrating their proficiency, (c) to stimulate the development of adequate training facilities, (d) to aid in evaluating residencies and fellowships under consideration for approval by the Council on Medical Education and Hospitals of the American Medical Association and (e) to advise physicians desiring certification as to the course of study and training to be pursued."[3]

These boards are not educational institutions, but they constitute a force that is profoundly modifying the course, the content, the cost and the duration of medical education today. These 19 boards have, up to June 30, 1950, certified 39,804 persons as competent specialists in these various fields. Each of these (with a few early exceptions) has been required to spend several years, after the internship, in approved residency or preceptor training. There is, I think, no doubt that this system has improved the level of performance in various fields, but it has created plenty of unanswered problems for medical schools and hospitals.

It is difficult to obtain fair figures on such a matter, but if one looks the country over it seems fair to assume that the burden of advanced medical education is not less than the burden of undergraduate education. In this rough calculation I include various forms of postdoctorate instruction preparing men for specialty practice, for research or for teaching, or offering them opportunity for keeping in touch with current developments. This great expansion (which really means that there are 50,000 students in medical schools, instead of 25,000) has never been brought into view with sufficient clarity, nor has due attention been given to its financing. But it is one of the reasons that members of medical faculties, though large in numbers, are heavily overburdened and that financial officers of medical schools have trouble sleeping.

Training directed toward research and teaching is still highly individualized. Smaller numbers are concerned, and great effort is made to prepare men for the period ahead and not for the period just past.

In general, postgraduate medical education, although it has grown tremendously during the half-century, is still of indeterminate pattern, and much hard thinking remains to be done.

Medical Education and the Community

Medical education exists as a part of local and national communities. It stands in close relation to many community activities, and closer to hospitals than to any other. A large part of medical teaching is actually carried out in hospitals. This relation, then, is more than co-operation and friendship: it is symbiosis. The factors in this symbiotic relationship, which is as vital to the hospitals as to the schools, need careful study and understanding. The past fifty years have seen hospitals and medical schools working both separately and together on their common problems. Both do better when they work together.

The Duration of Medical Education

There is general agreement concerning the necessary duration of medical education; it goes on as long as one lives. There is no such agreement about the formal portion, regarding that as running from entry into medical school to the assumption of independent activity in one's chosen field. It is currently a long process; indeed, what other educational program is as long?

About three fourths of the students in medical schools have college degrees. Their average age at entering medicine (in my own experience and in peacetime) is ± 22 years. That means the M.D. at 26, and independent activity (after a postgraduate program of usual length) at 30 or 31. If military service is required of every young doctor, this figure will be 32 or 33. The advantages of this long process have been mentioned; since this is a current problem of medical education, it is necessary to refer to some disadvantages as well.

First, prolonged education is expensive for the schools and for students. Because of the cost, many able workers are lost to medicine.

Secondly, the duration itself, aside from the monetary cost, keeps some good men out of medicine. To many vigorous personalities, postponement of responsible participation does not appeal.

Third, as President Lowell pointed out in an article in this journal in 1940,[4] to bring men to independent work at 30 or 33 may, for some of them, cut out the most original and constructive period. Thomas Lewis published *The Mechanism and Graphic Registration of the Heart Beat* at 28.

Finally, the longer the preparation, the shorter the term of professional activity.

No one is willing to accept poorer training, but the question is this: Can the patient application of intelligence and imagination lead to a rearrangement of the total educational program that will give us mature and well trained doctors at a younger age? I believe it can, and that this is a major responsibility for the leaders of medical education.

The Cost of Medical Education

This is a gloomy heading for a terminal section but an important aspect of these fifty years of history. It was apparent early in this half-century that a tuition fee that could be borne by the student was not enough to do the job that was required. Costs rose further, as the task of the medical school expanded, through the growth of research, the development of postgraduate teaching and other factors. The gap between reasonable tuition and the cost per student has continued to grow, especially in recent years. In 1910 tuition fees were sufficient to meet about 70 per cent of the costs of medical education; in 1950 tuition collected accounts for only about 25 per cent of the cost of medical schools. Thus, American medical education is now faced with a financial crisis at the moment of its greatest promise and responsibility.

In the period of 1949 to 1950 the responsibility for medical schools was held as follows: 3, by municipal governments; 35, by state governments; 41, by tax-exempt private corporations. None of these groups are free of financial anxiety.

This problem of rising costs has been further complicated by a falling income rate on endowments. In 1900 most financial support of medical schools other than tuition came from generous persons who were concerned with the progress of medicine and medical education. In the last twenty years gifts from individual donors have been supplemented by those from foundations, from industry, from special societies and from various governmental sources. These last have been given mainly for the support of special activities, such as research, and are for the most part unavailable for the general purposes of the institution. Even with these additions, it is now clearly necessary for the medical schools of the country to seek emergency financial aid from the Federal government for their general operating expenses. The obvious disadvantages that may be associated with this source can be avoided if Federal support is balanced or more than balanced by increased private support. What are some possible sources of such increased private and nonpolitical support of medical education? One such source is described in the following paragraph from O'Hara's admirable recent article, "Today's Trends in Medical Education"[5]:

> A voluntary agency known as the National Fund for Medical Education has been incorporated. Its board of trustees includes outstanding examples of the nation's powerful business, labor and professional leaders. The National Fund embraces an imaginative concept of corporate citizenship and philanthropy; it conceives of a system in which the great industrial and mercantile corporations of America would voluntarily support medical education as a national enterprise. Such support might permit the free survival of a function that was formerly dependent upon private philanthropy, but is now in danger of having to choose between modest governmental subsidy or extinction. If medical and allied science can turn toward this sort of corporate philanthropy, the possible disaster of government control might be converted into a triumph of democracy and a continuation of educational freedom in medicine. Obviously this is more easily said than done but the founders of the National Fund seem to be convinced that they can contrive a way of doing it, and within the next few years we may see this great effort consummated in a substantial investment of America's brains and resources in medical education.

Since this will be an organization seeking only to help medical education and not to control it, it will offer an avenue of approach for those who may wish to contribute to the support of medical education and research on a broad basis. This would supplement and not conflict with existing direct individual giving.

A natural source of funds for the support of medical education is to be found in the graduates of medical schools. The careers of these graduates are based on the educational opportunity they enjoyed as medical students. Because the cost of medical education is several times that of the tuition (expensive as tuition must seem to medical students and their parents) every medical student is in the position of having received from his university a large scholarship during every year of his medical course. We all know what munificent salaries interns and residents receive, and no one expects medical-school graduates in their first five years to give large gifts to the medical school, but we also know that many physicians' earnings may later permit them to repay some of their obligation to the society that provided them with educational opportunity and thus permit them to make possible similar opportunity for a later generation. Federal aid, which I believe to be necessary as an emergency measure, cannot be permitted to be the entire solution of the present financial quandary of medical schools. It appears to me that the freedom, the success and quite possibly the survival of medical education as we know it will depend to some degree on the significant participation of physicians in the financial support of medical education. It is sometimes suggested that contributions from physicians can only be a drop in the bucket. This is not in accord with the arithmetic of the situation. There are something like 180,000 physicians in the United States. Even if we subtract 40,000 to rule

out the recent graduates and the retired and inactive ones, we have 140,000 left. One hundred dollars per physician per year returned to medical schools from this group would increase the total income of medical schools by $14,000,000 per annum. This is equal to the income at 4 per cent on $350,000,000 of endowment. If it could be made a continuing, habitual contribution, it would be the best possible guarantee of the freedom and the continuing quality of medical education in this country.

If this plan develops, most physicians will naturally wish their contributions to reach their own schools directly through alumni funds or other established mechanisms. Others may wish to give to a more impersonal organization, such as the National Fund for Medical Education or funds collected in other ways. The ideal formula, from my point of view, is adequate support without strings. Therefore, in selecting a channel for giving, alumni will do well to select one as free as possible from the dangers and inefficiencies of political control.

In addition to the financial plight of medical schools there is another problem: the financial plight of individual medical students and individual young physicians. To pay tuition until the age of 26 or later, to be essentially a nonearner till 30 or later, is a difficult assignment, not easily taken on by members of large families or by those in lower income brackets. This situation is dangerous to medicine in that it keeps some able men away from medicine and may mean that the recruitment of our profession will come from a small percentage of the population. The answer to this part of the problem appears to be a proper scholarship program, based on improved methods of selection for *both ability and character*.

Conclusion

The period 1901 to 1950 has been a period of violent change in medical education in the United States and throughout the world. Because of the worldwide changes, medicine in the United States has greater responsibilities and greater opportunities than it has ever had before. Medicine in general can offer to a vexed and troubled world more than it could ever offer before. If the potentialities of medicine for the future are to be realized the lessons of the past must be well learned, and planning for the future must be done with wisdom. Medicine must be developed through the recruitment of superior persons, through the organization and integration of the community to supply the opportunities of medical education and through generous financial support. The medical education of the future will be based on the experience of the recent past, so that the real test of the progress of the last fifty years will be the next fifty years.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 37181

PRESENTATION OF CASE

First admission. A twenty-four-year-old girl entered the hospital because of swelling of the legs.

Diabetes was first diagnosed in this patient at the age of ten, the disease having been discovered after an illness of several months' duration that was characterized by weakness, weight loss and polyuria, culminating in coma. She was admitted to another hospital, where the coma responded to therapy. She was placed on insulin and a strict diet and discharged improved. During the ensuing years she failed to follow this regimen carefully, partly because of social difficulties. Her parents had been divorced when she was six years old, and thereafter she had no home of her own. She boarded with a family next door to her mother's place of employment as housekeeper and in the winter lived with a married sister in Florida, where her mother also went with the family for whom she worked. Since the family with whom she lived was often away, the patient had to fend for herself. She had few insulin reactions but had four additional episodes of coma, apparently brought on by dietary indiscretions. Ordinarily, however, the urine tests were green to yellow on a regimen of 25 units of protamine zinc insulin daily. Although she tended to be chronically ailing she was graduated from high school. She worked for a month or two afterwards as a file clerk in a bank but soon gave this up because of fatigue. She habitually stayed in the house during the day and went out to movies with her mother or with friends at night.

Seven years prior to entry she suddenly developed diarrhea, which continued relentlessly. This was characterized by the passage of 3 to 4 loose, bulky, foul-smelling nonbloody stools each day, usually in the evening, when it seemed to be worse. On the worst days she passed as many as 8 stools. Paregoric, belladonna, bismuth and numerous similar preparations had been tried without success. Four years prior to entry amputation of the left middle toe was performed because of an infection.

Three years before admission she consulted her physician because of the small size of her breasts, of which she was painfully conscious. He prescribed one stilbestrol tablet daily for fourteen days of each month, followed by one Pranone tablet daily for seven days. On this regimen she had her first menstrual period, and subsequently she had withdrawal periods every two to three months. The breasts, however, failed to enlarge. Six weeks before admission the patient noted swelling of the feet and legs, headaches and failing vision. She was admitted to another hospital, where she was told she had "kidney trouble." The edema of the legs gradually subsided and after two weeks she was discharged. At home her vision deteriorated so much that she was no longer able to read. One week before entry she began to vomit intermittently. Food seemed to give her a "stomach ache," which was relieved by vomiting. She continued to take 26 units of protamine zinc insulin daily. About four days before entry the swelling of the legs recurred and the headaches became more severe and the vision less distinct.

There was no history of Bright's disease, blood in the urine, pyelitis or scarlet fever. The family history was noncontributory except for the occurrence of diabetes mellitus in a maternal uncle.

Physical examination showed a thin, pale woman who was able to breathe comfortably lying flat in bed. The eyelids and cheeks were puffy. The pupils were of average size but were slightly irregular. They were fixed to light but did react in accommodation. The margins of the optic disks were obscure but not elevated. The retinal arterioles showed diffuse narrowing, and the veins appeared tortuous and dilated. Hemorrhages and fluffy exudates were scattered throughout the fundus. A few hemorrhages were small and round, the majority large and flame-shaped. The neck veins were distended and the breasts infantile. The heart was enlarged 10 cm. to the left of the midsternal line and a presystolic gallop was audible just inside the apex. The liver edge was palpable 2 fingerbreadths below the right costal margin on deep inspiration. There was ++ edema of the feet and legs extending to the knees and + sacral edema. The left middle toe was missing and a pustular ulcer 1 cm. in diameter was present over the head of the right first metatarsal bone. Dorsalis pedis pulses were vigorous bilaterally, but no posterior tibial pulsation could be distinguished. The knee jerks were hypoactive and ankle jerks absent. The uterus was infantile, measuring approximately 3 cm. in length. Axillary and pubic hair were scanty.

The temperature was 98°F., the pulse 95 and the respirations 20. The blood pressure was 176 systolic and 118 diastolic.

The urine had a specific gravity of 1.017, gave a +++ test for albumin and contained 4 to 9 white cells and 2 to 5 red cells in the sediment. It showed an olive color reaction in a sugar test. Examination of the blood disclosed a hemoglobin of 8.4 gm., a red-cell count of 2,700,000 and a white-cell count of 9600, with 83 per cent neutrophils. A bone-marrow aspiration showed intense erythroid hyperplasia. The carbon dioxide was 20.8 milliequiv., the sodium 134.2 milliequiv., the chlorides 102 milliequiv. and the potassium 4.8 milliequiv. per liter; the cholesterol was 344 mg., the phosphorus 3.7 mg., the total protein 4.83 gm., the albumin 2.84 gm., the globulin 1.99 gm., the calcium 8.0 mg., the iron 162 microgm., the alkaline phosphatase 5.0 units, the nonprotein nitrogen 29 mg. and the fasting blood sugar 74 mg. per 100 cc. A Congo red test showed 73 per cent retention in the serum in one hour. A urea clearance test was 11 per cent of normal and a phenolsulfonphthalein test showed 15 per cent excretion in one hour and 30 per cent in two hours. The urinary protein was 2.2 gm. per twenty-four hours. A urine culture grew abundant gram-negative rods and abundant yeasts. A Sudan III stain of the stool showed a very small amount of fat. Other stool studies were negative for parasites or pathogens but revealed the presence of undigested meat and vegetable particles. Duodenal drainage showed decreased amounts of trypsin, amylase and lipase but other tests of pancreatic function, including analyses of the stool fat and nitrogen content, and the blood amylase responses after fat and prostigmine were normal. Sigmoidoscopy was negative. The basal metabolic rate was −17 per cent and the protein-bound iodine 8.0 microgm. per 100 cc. Urinary 17-ketosteroids were 2.2 mg. per twenty-four hours and FSH negative for 6.5 mouse units per twenty-four hours. A vaginal smear revealed low estrin effects. A roentgenogram of the chest indicated that the heart was somewhat prominent in the region of the left ventricle and the aorta was tortuous. The hands, spine and long bones showed some decalcification. A plain film of the abdomen was negative and a barium-enema examination showed fine irregularity of the bowel margins. A gastrointestinal series revealed prominent mucosal folds and an increased rate of passage of barium through the small bowel.

In the hospital the patient was placed on a low-sodium and 40-gm.-protein diet and given 10 to 25 units of protamine zinc insulin daily plus small doses of crystalline insulin by test. The ankle edema decreased, but the diarrhea persisted. Five other urinalyses gave +++ tests for albumin and showed specific gravities of 1.010, 1.006, 1.010, 1.009 and 1.016. When the dietary protein was increased to 80 gm. the nonprotein nitrogen rose to 50 mg. per 100 cc. It was believed that the patient was approaching a terminal condition. She was discharged on the nineteenth hospital day feeling somewhat better. The prescribed regimen consisted of a low-sodium, 40-gm.-protein diet, 18 units of protamine zinc insulin daily, crude liver extract, iron and ascorbic acid.

Second admission (five weeks later). In the interval the patient remained in bed most of the time and felt fairly well until about two weeks before entry, when intermittent nausea and vomiting recurred. During the last two days she had very little appetite and was able to retain only fruit juices. Her condition became progressively worse, and her physician sent her back to the hospital for intravenous feedings.

The physical examination showed no significant changes from that of the previous admission.

The urine had a specific gravity of 1.008 and gave a ++++ test for albumin; the sediment was loaded with white cells. The white-cell count was 9500, with 85 per cent neutrophils. The blood sodium was 117.4 milliequiv., the chlorides 87 milliequiv., the carbon dioxide 21.0 milliequiv. and the potassium 4.8 milliequiv. per liter. Other chemical determinations were essentially as before. The fasting blood sugar ranged between 58 and 530 mg. per 100 cc. The nonprotein nitrogen, which was 60 mg. per 100 cc. on admission, gradually rose to 123 mg. per 100 cc. At one point the serum sodium fell to 109.3 milliequiv. and the potassium rose to 8.6 milliequiv. per liter. Both values responded somewhat to infusion of hypertonic (3 per cent) sodium chloride, salt-poor albumin, dextrose and water. The last serum chemical determinations, obtained six days before death, showed the sodium to be 136.5 and the potassium 6.0 milliequiv. per liter.

Despite administration of digitalis and antibiotics the patient's course was steadily downhill, with increasing rales in the chest, abdominal distention and decreasing urinary output. During the last eight days of life the urinary output averaged slightly less than 500 cc. a day. The white-cell count rose terminally to 19,000 and the patient died quietly on the thirtieth day.

Differential Diagnosis

Dr. Allan M. Butler*: There was so much laboratory data in this patient's record that Dr. Castleman presented me with the original record in addition to the abstract.

Diabetes was first diagnosed when the patient was ten years old, so she had had diabetes for fourteen years. The record would lead one to believe that she was treated with protamine zinc insulin alone and a "strict diet." I am not told what the "strict diet" was, but it does not matter, because she failed to follow it, partly due to social difficulties. Her many social difficulties were probably an important factor in the poor control of the diabetes. Her parents were divorced, and she apparently was lonely and hung around the house without

*Chief, Children's Medical Service, Massachusetts General Hospital.

much incentive to take care of herself. The fact that she was given protamine zinc insulin alone and had insulin reactions and episodes of coma show that she was subject to wide fluctuations of blood sugar. The record actually shows that she had occasional rather than a few insulin reactions. The fact that she was chronically sickly is further evidence that the diabetes was not well controlled or that there was some complicating factor, because diabetics should not be chronically sick. In addition to the poorly controlled diabetes, I should guess that she had some nutritional deficiencies and a deficient storage of glycogen.

A poorly treated diabetic can develop diabetic neuritis very early in the course of the disease. This patient probably had diabetic neuritis; hence her fatigue. There are two things of note: One, there was very little pain, which is usually a rather prominent symptom of diabetic neuritis; two, in diabetics who have this degree of degenerative changes, calcification of the veins is usually found in the x-ray films, but apparently none was seen. The good dorsalis pedis pulses and the absence of the posterior tibial pulses were consistent with the circulatory disturbance in diabetic neuritis due to sympathetic nerve involvement. Then, also, on her worst days, the patient passed as many as eight stools. Such diarrhea occurs with diabetic neuritis. Rundles[1] wrote an excellent review of the subject, and Sheridan and Bailey[2] discussed the response of the diarrhea to liver therapy. Diarrhea also may be associated with pernicious anemia, which may occur in diabetics and has been described by Root and others.[3] The Argyll–Robertson pupils were also probably part of the diabetic neuritis. The prominent mucosal folds and increased rate of passage of barium through the small bowel revealed by the gastrointestinal series were consistent with neuritis affecting the autonomic nervous system and sympathetic ganglia, with nutritional deficiency or with pancreatic insufficiency.

The eyes showed the changes recorded in the history, but in addition an ophthalmologist found Grade II to IV hypertensive retinopathy as well as the diabetic retinitis, characterized specifically by multiple aneurysms of venules, which are the source of hemorrhage.

I suppose that the retarded development was the result of a metabolic disturbance rather than of a primary adrenal or pituitary deficiency. However, Simpson[4] has described diarrhea as part of an adrenal insufficiency that may be associated with diabetes. The abundant yeast in the urine raises the question of moniliasis, which may be accompanied by adrenal insufficiency, but on culture the yeast apparently was not monilia. The low basal metabolic rate, which was against pheochromocytoma, was consistent with an adrenal or pituitary insufficiency, but it was also compatible with marked debilitation due to multiple metabolic disturbances. The high blood pressures were against adrenal insufficiency as a complication of the diabetes. The small insulin requirement — 10 to 25 units of protamine zinc insulin daily plus small doses of crystalline insulin by test — was, however, suggestive of adrenal insufficiency.

On admission the urine gave an olive-green sugar reaction. The amount of sugar in the urine is not a very good index of the blood sugar in such a patient, as the renal threshold is probably elevated.

The hemoglobin was 8.4 gm., with a red-cell count of 2,700,000, but the indices were not suggestive of a macrocytic anemia. There was no evidence of megaloblastic arrest or macrocytosis. The normal white-cell count is against pernicious anemia.

The ionized calcium was normal, although the total serum calcium was low because of the low serum-protein concentration. The alkaline phosphatase of 5.0 units and the nonprotein nitrogen of 29 mg. per 100 cc. were unexpectedly good; the latter may have been due to the fact that the patient was on a very low protein diet.

The abstract stated that a phenolsulfonphthalein test showed 15 per cent excretion in one hour and 30 per cent in two hours, but the record gave this as follows: 6 mg. intravenously; 15 minutes 50 cc., less than 1 per cent; 30 minutes 45 cc., 1 per cent; 60 minutes 45 cc., 13 per cent; 120 minutes 55 cc., 15 per cent. Unless the urea clearance and phenolsulfonphthalein tests were done on catheterized specimens, they may be misleading, as a patient with diabetic neuritis may be unable to empty the bladder. The low values were not consistent with the intravenous pyelogram of a month previously — unless there had been a very rapid progression of renal disease in a month. Were these tests done on catheterized specimens?

A Physician: They were done on specimens obtained by voluntary voiding.

Dr. Butler: Then I have not too much confidence in them.

During the first admission the patient was placed on a low-sodium diet. Such a diet requires very careful following of such a patient, as she may have been unable to conserve sodium and chloride in the presence of the diminished renal function. Five weeks later depletion of sodium and chloride had occurred, as indicated by the serum sodium of 117 milliequiv. and the chloride of 87 milliequiv. per liter. At that time the potassium was normal but in the course of the next three days rose to 7 milliequiv. per liter in spite of the fact that the patient was receiving parenterally administered fluids and dehydration was improved. The nonprotein nitrogen, which was 60 mg. at the time of the final admission, rose to 123 mg., the sodium fell to 190.3 milliequiv. and the potassium rose to 8.6 milliequiv. Cardiac failure seems to have played a part in the steady downhill course.

The 18 units of protamine zinc insulin on which the patient was discharged from the hospital at the first admission is not an optimal dose for a patient who was subject to wide fluctuations of blood sugar and had a high renal threshold. A smaller dose of protamine zinc insulin with doses of crystalline insulin immediately preceding each meal would have been preferable. Use of vitamin B-12 orally, with or without folic acid, instead of liver extract deserves consideration. The gastrointestinal absorption may have been improved by using one of the potent pancreatin preparations, such as Viokase, put out by the Vio Bin Corporation.

Although it was not stated in the abstract, the diagnoses in the record of the other hospital were diabetes mellitus, diabetic retinitis, chronic pyelitis and intercapillary glomerulosclerosis. I can certainly confirm those diagnoses.

This did not seem like a uremic death or one due to circulatory failure or adrenal insufficiency. No data was given on the bleeding time, clotting time or capillary fragility. I am sure that there was increased capillary fragility with a bleeding tendency, so I wonder about the possibility of intracranial hemorrhage.

I think that there was more renal damage than the pyelogram of two months ago suggested and that there was a rapidly progressing terminal necrotizing pyelonephritis, intercapillary glomerulosclerosis, cloudy swelling of the tubules and fatty degeneration. Neuritis and vascular changes may also have caused adrenal or pituitary changes in the last days or weeks of life. In addition, I think there was a gastritis, erythroid hyperplasia of the bone marrow, islet-cell changes of the pancreas, possible changes in the acinar cells and an atheromatous aorta. There probably was fatty degeneration of the liver, particularly around the central veins. Diabetic neuritis in the peripheral and spinal nerve roots and associated tracts and changes in the cells of the central nervous system were probably present. There may have been changes reducing the functioning capacity of the pituitary and adrenal glands as the result of hemorrhage, degenerative changes or atrophy.

One wonders how much the neuritis affected the intestinal absorption and how much the absorption affected the neuritis by contributing to the diet deficiency.

Although this is not the time nor the place, we should be more concerned about the so poorly defined causes of the degenerative changes from which this patient suffered during life than about the findings at death. At the moment, however, Dr. Castleman will tell us the end results of these degenerative changes and why this patient died.

Clinical Diagnoses

Diabetes mellitus.
Intercapillary glomerulosclerosis.
Diabetic neuropathy.
Diabetic retinitis.
Pyelonephritis.

Dr. Butler's Diagnoses

Necrotizing pyelonephritis.
Intercapillary glomerulosclerosis.
Gastritis.
Erythroid hyperplasia of bone marrow.
Changes in islet cells and acinar cells of pancreas.
Fatty degeneration of liver.
Diabetic neuritis, peripheral and spinal.

Anatomical Diagnoses

(*Diabetes mellitus, severe.*)
Intercapillary glomerulosclerosis, severe.
Necrotizing renal papillitis, bilateral.
Pyelonephritis, bilateral.
Ascites.
Hydrothorax, bilateral.
Pulmonary edema.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy showed a great deal of fluid everywhere in the body. The abdominal cavity contained about 4 liters and the pleural cavity about 2 liters; the lungs were filled with fluid. The heart was not very much enlarged and weighed only 270 gm. It was not at all remarkable on microscopical examination. We could find no evidence of an increased amount of fat. The glycogen seemed to be somewhat increased in the myocardial fibers.

The pancreas at gross examination was not abnormal, but on microscopical examination there was not a single islet cell. Ordinarily, the changes in the islet cells consist in hyalinization or hydropic degeneration, but all that was found was diffuse scarring throughout the pancreas — little foci of connective tissue where I suppose islets had been at one time. A special stain for the beta granules was ineffective, because the specimen was taken too long post mortem. The adrenal glands were normal in size and microscopically showed a great deal of fat, which indicates that there was very little if any depletion in the adrenals.

The kidneys were interesting. There was, as Dr. Butler predicted, a papillary, necrotic type of pyelonephritis. The tips in about half of the pyramids were completely necrotic. This was not, however, a very severe papillitis, but there was a moderately severe degree of intercapillary glomerulosclerosis. In almost every glomerular tuft extending from the capsule, and sometimes filling the glomerular space, was an accumulation of material that I thought at first was fluid and believed might be related to the albumin that the patient had received. In some areas this material showed beginning organization and suggested the crescent of the ordinary nephritis

(Figure 1). A Masson stain showed some connective tissue in it, but fat stains were also positive. Dr. Agustin Roque, of our histochemical laboratory, showed that this material located in the capsule and in the glomerular space was cholesterol esters. Practically every tuft was involved. Apparently in the original description of intercapillary glomerulosclerosis by Kimmelstiel and Wilson[5] the same findings were described in the tufts. I have never seen it before. These cholesterol esters must have remained localized in the tuft long enough to stimulate

FIGURE 1.

a connective-tissue response and may therefore have added to the renal insufficiency.

DR. ALFRED KRANES: How about the rest of the pancreas?

DR. CASTLEMAN: The acini were all right.

DR. BUTLER: The extensive destruction of islet tissue may possibly have been related to the low insulin requirement. Maybe, if there is enough destruction of pancreatic tissue, it does away with the hyperglycemic factor. Furthermore, if a sympathectomy is done in a diabetic, the insulin requirement may be lowered.

DR. MADELEINE BROWN: Were the nerves examined?

DR. CASTLEMAN: I looked at some of the nerves; they appeared normal. Other sections are being studied by Dr. Charles S. Kubik.

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CASE 37182

PRESENTATION OF CASE

A seventy-three-year-old woman entered the hospital complaining of abdominal pain.

Until nine weeks before admission the patient had been very active in spite of chronic fatigue and rheumatoid arthritis of many years' duration. At this time she first noted the onset of gnawing, nearly constant nonradiating midepigastric pain, which was frequently aggravated by food. Her usual fatigue became more pronounced, but she had no anorexia or change in bowel habits. Six weeks and again three weeks before admission she was seen in the Out Patient Clinic, where she was given phenobarbital aspirin and vitamins without relief. Two weeks before entry a gastrointestinal series taken at another hospital showed only a few densities in the lower abdomen compatible with calcified fibroids. About this time she developed severe anorexia, losing seven pounds in the course of her illness. Ten days before admission she took to her bed because of extreme weakness. Her last normal bowel movement was seven days before entry, after which she became obstipated. Four days before admission she became jaundiced. The following day she noted large protruding hemorrhoids.

The past history revealed a left simple mastectomy performed for "tumor" thirty-two years previously. For many years she had had episodic pain, redness, swelling and heat in the finger joints, elbows, knees, feet and spine, which had been treated with large doses of aspirin. Prior to her illness she had a good appetite and regular, normal bowel movements. There were no symptoms suggestive of cardiac or respiratory disease.

Physical examination revealed a markedly dehydrated, cachectic woman with warm dry skin and a markedly distended abdomen. The left breast had been removed. The scleras were icteric. The anterior nasal septum was perforated and covered with malodorus crusts, which were consistent with atrophic rhinitis. A small lymph node was felt in the left anterior cervical triangle. The anteroposterior diameter of the chest was increased. Both lung

bases and the right chest to the level of the third thoracic vertebra were dull to flat, with decreased tactile fremitus and decreased to absent breath sounds. A few rales were heard at the left base. The heart was not enlarged to percussion; the rhythm was regular. A Grade II systolic apical murmur was not accompanied by a thrill. A tender mass was indistinctly palpable in the midepigastric area, and the liver dullness extended to the level of the umbilicus. A fluid wave was demonstrable, and there was a small umbilical diastasis. An occasional peristaltic tinkle was heard. The extremities showed changes suggestive of rheumatoid arthritis. The dorsalis pedis pulses were not palpable. Neurologic examination was negative. Pelvic examination revealed procidentia and a very small uterus. No adnexal masses were felt. Rectal examination confirmed the presence of a rosette of large thrombosed internal hemorrhoids.

The temperature was 99.6°F., the pulse 120 and the respirations 20. The blood pressure was 125 systolic, 80 diastolic.

The urine gave a + test for albumin, a + test for bile and a green sugar reaction; a few hyaline casts were seen in the sediment. Examination of the blood showed a hemoglobin of 14 gm. and a white-cell count of 9700. One yellow, semiformed stool was guaiac negative. The blood Hinton test was negative. The sodium was 130.4 milliequiv., the potassium 4.0 milliequiv., the chlorides 97 milliequiv. and the carbon dioxide 24 milliequiv. per liter. An electrocardiogram was within normal limits. A chest film showed bilateral apical caps. The right leaf of the diaphragm was elevated, and there was atelectasis in the adjacent segment of lung. The heart was of normal size. The aorta was partially calcified. A plain film of the abdomen showed probable hepatomegaly and possible splenomegaly. The renal outlines were unremarkable. There was scattered gas in both large and small bowel. A few loops of small bowel in the midabdomen were at the upper limits of normal size. No point of mechanical obstruction was demonstrated. All the bones were somewhat atrophic, and there was wedging of the thoracic vertebras.

A few hours after admission the patient began to have frequent small loose bowel movements and vomiting, because of which a Levine tube was passed. The abdomen was noted to be diffusely tender without localization. A total of 250 mg. of demerol and 2.0 gm. of chloral hydrate was administered in an effort to relieve the discomfort. The patient also received 0.4 mg. of digitoxin and 0.8 mg. of cedilanid, with intravenous infusions of 3000 cc. of a 5 per cent solution of dextrose in physiologic saline and 1500 cc. of dextrose in water. The jaundice became quite deep, and she died suddenly twenty-four hours after admission, her heartbeat stopping before her respirations.

Differential Diagnosis

Dr. Perry Culver*: I am quite confused by this case. It seems to me that a great deal of material is irrelevant. After cutting away the underbrush, I believe it adds up to a case of an old woman with a past history of rheumatoid arthritis who developed a rapidly progressive disease of perhaps nine weeks' duration. There were only a few salient facts pointing to the nature of this disease. Of these salient facts, the ones I can put the most weight on were the presence of a large liver with jaundice and the peculiar episode that preceded death.

The midepigastric pain suggests a number of conditions that might involve the stomach — hypertrophic gastritis, atrophic gastritis and cancer of the stomach, — but it would be somewhat unusual for symptoms of gastritis to be aggravated by food. The anorexia, which appeared two weeks before admission, was consistent with cancer of the stomach or the pancreas, hepatitis and a number of other conditions; it was nonspecific. The extreme weakness may have been due to failure to take food; the patient was old and probably decrepit, anyway. However, it too was suggestive of such conditions as carcinoma of the pancreas. The sudden change in bowel habits from normal to obstipation in one week's time I find extremely puzzling. Did it mean that there was obstruction, a paralytic ileus or a perforation and peritonitis due to gallstones?

Jaundice appeared in four days and became very deep within a period of six days. That is one of the facts upon which I am putting a great deal of weight. The large hemorrhoids suggested increased portal pressure, increased intra-abdominal pressure or perhaps even disease in the colon itself. However, there was no history to suggest an intracolonic disease such as ulcerative colitis, which is often seen with hemorrhoids. I think an increase in portal

*Assistant physician, Massachusetts General Hospital.

pressure is the best explanation for the hemorrhoids. The marked distention of the abdomen may have been due to obstruction or may have been associated with severe intrahepatic disease, such as the terminal stage of cirrhosis. The patient may have had metastases spreading throughout the abdomen.

Whether or not the lymph node in the left anterior cervical triangle was significant, I cannot say. Nevertheless, I think I shall consider it as a sentinel lymph node for carcinoma of the stomach or possibly retroperitoneal cancer. The findings in the lungs may have been due to fluid, but with an enlarged liver, fluid in the abdomen and a cardiovascular system normal for a patient of her age I believe there was elevation of the diaphragm rather than that fluid was present. Whether the fluid wave described was a real finding or not, time will tell. It is sometimes tricky to demonstrate a fluid wave.

The laboratory findings really gave me very little help. The + test for albumin in the urine, the long history of rheumatoid arthritis and the enlarged liver might make me think of amyloid disease; but a + albumin and casts could also have been the urinary findings in a patient who was extremely dehydrated. I do not think I can put too much weight on that. However, the positive test for bile in the urine was confirmatory evidence that the patient had a regurgitation jaundice and not a hemolytic jaundice. The hemoglobin of 14 gm. and the white-cell count of 19,000 were probably due in part to the dehydration. Although I am not told what the differential count of the white cells was, I suppose it was normal. At any rate, there was no evidence of bleeding in the gastrointestinal tract or of loss of blood anywhere else. That helps me to rule out lesions of the gastrointestinal tract, such as carcinoma of the large bowel, stomach or ampulla of Vater. The yellow semi-formed stool does not help me a great deal; the negative guaiac test does. The normal electrocardiogram is of considerable comfort in that it shows me that she did not have any long-standing cardiac disease. The blood electrolytes — I doubt if they have any bearing on the diagnosis.

May we see the x-ray films now, please?

DR. JOSEPH HANELIN: There is very little to add to the description of the films as given in the protocol. The right diaphragm is considerably elevated, and the lungs themselves are clear except for the basal atelectasis on the right. The heart is normal in size. There is evidence of liver enlargement.

DR. CULVER: Can you see the spleen at all?

DR. HANELIN: It is not appreciably enlarged; it is a borderline size. There are a few gas-filled loops of bowel — not really enough to indicate a mechanical obstruction. There is gas in both small and large bowel. A vague density in the left pelvis may be due to calcification, possibly within a fibroid. All the bones are osteoporotic and there is some compression of a number of the vertebras.

DR. CULVER: Not more than you would expect for a woman of this age?

DR. HANELIN: Not more marked than usual and not enough to suggest that it is due to metastatic cancer.

DR. CULVER: The next turn of events, the sudden development of frequent loose stools and vomiting that began after admission, I am at a loss to explain. Were these symptoms due to the development of a partial obstruction, to the natural progression of a disease that involved all the organs of the abdomen or, by chance, to the digitalis? I am curious about why the patient was given the digitoxin and the cedilanid. I suppose the physicians were trying to protect her cardiovascular system while giving her large amounts of fluid to combat the dehydration.

Then sudden death occurred. I do not know the significance of the heart's stopping before the respirations. I suppose it could mean she had a sudden heart block due, perhaps, to digitalis.

The large liver is the most important clue to the diagnosis. The patient had a rapid downhill course, jaundice and a liver of the size that is usually seen with metastatic disease. Amyloid disease is the other possible explanation for a liver as large as this was. Other types of intrahepatic disease, such as hepatitis, do not produce such a large liver. There was no evidence to suggest an obstructive jaundice.

Consequently, metastatic disease of the liver is my first choice. What type of metastatic disease would produce this rapid downhill progression without evidence of its being found in the gastrointestinal tract? The sudden onset of anorexia and epigastric pain, the weakness and loss of weight are the vague, nonspecific findings that are usually present with carcinoma of the pancreas. Because carcinoma

of the pancreas cannot be ruled in or out, and because it frequently metastasizes to the liver, I think the pancreas was the primary site. Metastases to the liver may be present for a long time without producing much jaundice or much evidence of dysfunction. I believe the patient had a lesion in the pancreas for a few months with metastases to the liver over a fairly long period of time until the liver was completely involved and jaundice appeared. Death was probably due to cardiac block from the digitalis and not to any other cardiac disease.

DR. RICHARD WARREN: I should like to ask Dr. Culver if he considered hemorrhagic pancreatitis as possibly causing this?

DR. CULVER: The thought had passed through my mind, but hemorrhagic pancreatitis would not cause such a large liver.

CLINICAL DIAGNOSIS

Adenocarcinoma of pancreas.

DR. CULVER'S DIAGNOSES

Carcinoma of pancreas with metastases to liver.
Cardiac block due to digitalis.

ANATOMICAL DIAGNOSES

Adenocarcinoma of body and tail of the pancreas, duct-cell type, with metastases to the liver.
Thrombosis of portal, splenic, superior mesenteric, superior hemorrhoidal and right-ovarian veins.
Infarction, proximal jejunum.
Infarction of the liver.
Jaundice.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: When the peritoneal cavity was opened at post-mortem examination, it was found to contain a considerable amount of blood-stained fluid. Further exploration showed that this was due to infarction of the jejunum just below the ligament of Treitz, which had been caused by thrombosis of the superior mesenteric vein. This thrombus was continuous with thrombosis of the portal and splenic veins. Additional thrombi were found in the superior hemorrhoidal and right-ovarian veins. The small bowel contained a great deal of rather fresh blood, but it had not passed the ileocecal valve; the large bowel contained only firm, normal-colored fecal masses. The body and tail of the pancreas were replaced by tumor, which microscopically proved to be a characteristic adenocarcinoma with extensive metastases to the liver. We did not find any evidence of organic disease in the heart.

I think it is fair to assume that the thrombosis in the portal system of veins coincided approximately with the sudden turn for the worse during the last week or ten days or perhaps with the time when the hemorrhoids suddenly became apparent. It may well have originated in the splenic vein because of pressure by the tumor and then extended into the portal and superior mesenteric veins. It is also interesting to remember that venous thrombosis is not infrequently associated with carcinoma of the pancreas.*

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OUT OF THE SHADOW

MASSACHUSETTS finally has rejected the Old-Testament injunction that it is right to take an eye for an eye, a tooth for a tooth and a life for a life. Lawmakers have long clung to one of the most vindictive tenets of the stern Puritan faith in a code of absolute values and suprahuman justice. But man is not now, perhaps, so sure as he once was that his judgment is God-given, nor is he so confident that the relation of the individual to society is as indissoluble as that of the rivet to the bridge. This Commonwealth is more strongly bound to the past than many, and it is all the more heartening that at least one of the fetters has been weakened if not severed altogether.

A bitterly opposed bill to give juries the right to recommend life imprisonment in cases of first-degree murder, with the juries' decision binding on the judge, has been signed into law by Governor Dever. A similar measure was vetoed by Governor Bradford in 1948, and Governor Saltonstall in 1943 killed one that would have left the decision solely to the judge. The new statute does not abolish capital punishment — nor does it break cleanly with vengeful morality, for it excepts those convicted of rape-murder, and it rules out parole. Yet Massachusetts at last has forsaken Connecticut, Vermont and the District of Columbia, where the death penalty still is mandatory.

Governor Dever and the General Court deserve praise for their progressive action in respect to this phase of the penal code. Certainly as deserving of honor is Mrs. Herbert B. Ehrmann, who has singlemindedly — and often almost singlehandedly — fought since 1927 to bring about the mitigation and eventual abolition of capital punishment in Massachusetts. Her husband, it might be noted, was counsel for Nicola Sacco and Bartolomeo Vanzetti.

The electric chair has cast a long shadow on the deliberations and decisions of countless murder juries in this state. Strong but inconclusive evidence has led juries to let palpable scoundrels go scot free rather than find them guilty of first-degree murder. The same doubt has influenced other juries to soften their verdict to murder in the second degree. And innocent persons probably have died for the crimes of others. Yet law-enforcement officers and prosecutors historically have opposed any change in the medieval law with the statistically invalid argument that the death chamber is a deterrent to murder.

Britain, the source of the legal heritage of this country, has decided that capital punishment is morally indefensible, or, rather, that crime and punishment are indeterminate variables and that there is no absolute yardstick by which one can be measured to fit the other.

A crust of bread stolen in hunger, an armed robbery staged to finance a lifesaving operation, a murder committed to end an adultery — where does degree end and kind begin? Most of us have learned

that petty larceny is something more than an object of moral indignation. May there not also exist the possibility of extenuating circumstances in premeditated murder that society is morally bound to weigh?

The apologies of justice, however ardent, will not restore life to an innocent man wrongly condemned and executed. A dead man, however guilty, can never be made a useful member of society, and his punishment can afford little satisfaction to his victim.

Massachusetts has recognized this, however belatedly. The Commonwealth may be proud of its new statute. Though it may be abused, as are all laws, one of society's most pagan weapons has been voluntarily cast aside.

WHAT PRICE EDUCATION?

The report published elsewhere in this issue of the *Journal* in which Burwell summarizes fifty years of change in the social and economic framework of medical education brings again to the fore one of the most urgent problems that confront medicine today. That is the cost of medical education, which has exceeded the subsidizing capacity of any presently committed voluntary agencies.

The cause for concern in regard to the ever increasing difference between income and expense is the difference itself, not the reasons for it. The reasons themselves are not far to seek: the application of the full-time principle in teaching, the depreciation in the value of the dollar, the growth of research, and the development of postgraduate teaching. All these factors have come to represent a serious problem since the turn of the century, when costs began to show their accelerating upward trend.

Higher education has never been conducted on a basis of financial gain, as was indicated by Dr. Frederick C. Shattuck in 1900, whose address to the graduating class of Washington University is quoted by Burwell:

> Remember that you are, every one of you, debtors to the Medical School, debtors even in the lower and pecuniary sense of the term, in that the fees you have paid for your instruction do not nearly represent its cost.

In 1910, nevertheless, fees still met about 70 per cent of the costs; forty years later they were meeting only 25 per cent as the costs went up and the income rates on investments went down.

The annual deficit today, as estimated by the Surgeon General's Committee on Medical School Grants and Finances on the basis of needs cited by the schools themselves, is about $40,000,000. At even a rock-bottom estimate, the additional income needed is calculated "in tens of millions and not millions of dollars."

These essential funds must be found — and of course will be found, for the nation is not bankrupt. The question is: How? In this respect the American Medical Association, through its recently incorporated American Medical Education Foundation and its own pump-priming appropriation of $500,000, has taken a challenging stand. Its purpose is to augment this sum with funds collected primarily from physicians and to work in conjunction with the two-year-old National Fund for Medical Education, Incorporated, a cat that some time ago grew too noisy to be kept in its bag.

The final resort, of course, is Federal funds — a resort, still more or less in the background, that seems very logical to some minds and completely abhorrent to others.

The American Medical Association, working constantly to promote the voluntary way, has finally crystallized its attitude as one of direct opposition to any form of Federal participation yet devised for the payment of actual teaching costs.

The Massachusetts Medical Society, more prudent if less conservative, according to its "Principles of Medical Care" based its acceptance of the idea of Federal assistance on the absence of

> any supervision or control over the admission of students, curriculum, teaching personnel or administration of such medical schools; except such supervision as may be necessary to insure that grants shall be expended solely for the purposes for which they are made.

This nation has reached a point in its evolutionary cycle at which the threat of bureaucratic control over its free institutions has become a very definite one. It is not merely the opposition of one administration against another that confronts the nation; a new phase in the endless sequence of human affairs has come upon it.

The only constant factor in history is change, and salvation of the organism or of the colony lies in its continuing adaptation to the changing environment. For old institutions are not necessarily perfect. Some of the great endowments that are now shrinking away may have had their origin in a ruthless exploitation by a relatively few persons of the country's wealth of men and materials.

In order to replace at least partially the aggregation of large individual gifts on which education and the charities once depended, the effort must now be made to secure as much as possible of the necessary income through the smaller contributions of many givers. It is an effort that must be made, deliberately and earnestly; for the exercise of spontaneous generosity should never be abandoned entirely in favor of the unemotional and involuntary support of all worthy enterprises through the medium of government decree.

If Federal assistance to medical education must be resorted to, as seems likely, caution dictates that it should be accepted without undue eagerness, in minimum measure and with all possible safeguards for freedom of thought and action.

THE BITER BIT

AN EXCHANGE of telegraphic amenities between Mr. Oscar R. Ewing, Federal Security Administrator, and Dr. Elmer L. Henderson, President of the American Medical Association, again demonstrates that he who laughs last laughs last. Facsimiles of the Western Union messages have been distributed by the directors of the National Education Campaign of the American Medical Association to the members of Congress and to goodness knows whom else.

Mr. Ewing, with his eye glued, as usual, to the medicine ball, led off with a telegram to the editor of the *Journal of the American Medical Association* in which he animadverted on the contents of the President's Page in the issue of the *Journal* of March 31.

> It quotes a sentence (he complained) from what you mistakenly call a current pamphlet, describing it as Mr. Ewing's directive. Any reputable scientific periodical verifies statements before publication. Elementary check would have revealed that pamphlet was written and issued in 1945, some two years before I became Federal Security Administrator. Checking would also have revealed that this pamphlet is not being currently distributed by Federal Security Agency, and has never had remotest authority as directive. Since you profess to be a scientific magazine interested in truth I suggest you retract the statement as publicly as it was made in the first place.
>
> OSCAR R. EWING, Federal Security Administrator
> Federal Security Agency, Washington, D. C.

This message was placed before the President of the American Medical Association, who found that, to a Kentuckian, it was composed mainly of fightin' words. His reply was as follows:

> We have your telegram of April 3, protesting a reference in the *Journal of the American Medical Association*, to a pamphlet issued by your office titled: "Common Human Needs, an Interpretation for the Staff in Public Assistance Agencies," from which I quoted the following passage: "Social security and public assistance programs are a basic essential for attainment of the socialized state envisaged in a democratic ideology, a way of life which so far has been realized only in slight measure."
>
> We note your denial of responsibility for the pamphlet on the grounds that it was published in 1945 before your tenure as administrator of that office. This denial, as you request, will be duly reported in the *Journal*. You are correct in assuming that as a reputable scientific periodical it is the habit of this *Journal* to verify statements before publication. The facts concerning my reference are these.
>
> The pamphlet in question was reprinted for distribution by your office in 1949, when the public record indicates you were in charge of the Federal Security Agency, its publications and its directives to employees. Five copies were received in the mail here last week, which indicates certain currency still. These all carry the imprint, "Government Printing Office, 1949." The fact that the report was first printed in 1945 would not seem to alter the further fact that you apparently have thought well enough of it to have it reprinted in 1949.
>
> We would suggest that if you wish at this time to disavow the principles expressed in the pamphlet, you will wish to do so in a formal statement to Congress, for as recently as February 26 this year, it was protested on the floor of Congress as a grave misuse of taxpayers' money to disseminate wholly un-American philosophies.
>
> In case it was without your knowledge that your office was reprinting and distributing such un-American directives during your tenure, you may wish to issue a public statement disclaiming responsibility for the material. If so, we shall certainly be glad to be helpful in giving such a statement further distribution through the *Journal*, for the medical profession will be sincerely interested in any such action.
>
> ELMER L. HENDERSON, M.D., *President*
> American Medical Association
> 535 North Dearborn Street
> Chicago

In this exchange of repartee Dr. Henderson seems not to have come off second best.

The current attitude at Chicago headquarters in regard to never-popular socialized medicine might be expressed in the paraphrase "I could not love thee half so little, loved I not Oscar less." But that would be indulging in personalities, which is a

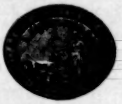
dangerous practice, jeopardizing both the dignity of the individual and the respect that his cause might otherwise command.

The question may be raised whether the public has not had enough of cock-fighting, edifying though it be, — and whether it would not like to see all parties concerned put an end to their Roman holiday and get on with life's more constructive activities.

Mention is made in the papers of a lady in Madison, Ind., lately coughing up a large horse-fly from the wind-pipe, which was probably lodged there last summer, though in what manner is not known. She immediately obtained relief from a most distressing cough and other painful and threatening symptoms.

Boston M. & S. J., *May 7, 1851*

MASSACHUSETTS MEDICAL SOCIETY



ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Georgian Room, Hotel Statler, Boston, on Monday, May 21, at 7:00 p.m.

Business:

1. Call to order at 7:00 p.m.
2. Presentation of record of meeting held February 7, 1951, as published in Supplement No. 1 to *The New England Journal of Medicine*, issue of April 5, 1951.
3. Reports of standing and special committees.
4. Report of Committee on Nominations:

President:	Dr. W. Richard Ohler.
President-Elect:	Dr. Thomas H. Lanman.
Vice-President:	Dr. Allen G. Rice.
Secretary:	Dr. H. Quimby Gallupe.
Treasurer:	Dr. Eliot Hubbard, Jr.
Assistant Treasurer:	Dr. Norman A. Welch.
Orator:	Dr. John Fallon.

5. Such other business as may legally come before this meeting.

Councilors are asked to sign one of the two attendance books before the meeting. The Cotting supper will be served immediately before the meeting.

H. Quimby Gallupe, M.D., *Secretary*

DEATHS

Hodskins — Morgan B. Hodskins, M.D., of Palmer, died on April 3. He was in his seventy-seventh year.

Dr. Hodskins received his degree from the University of Vermont College of Medicine in 1899. He was formerly the general superintendent of Monson State Hospital, and a member of the staffs of Wing Memorial and Springfield hospitals. He was a member of the American Psychiatric Association, the Boston Society of Psychiatry and Neurology, the Massachusetts Psychiatric Society and the New England Society of Psychiatry, and a fellow of the American Medical Association.

His widow, a daughter, a son and three grandchildren survive.

Weiksner — Francis A. Weiksner, M.D., of Worcester, died on April 10. He was in his fiftieth year.

Dr. Weiksner received his degree from the University of Lithuania in 1929. He was Worcester police surgeon for eight years before he retired last fall.

His widow and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

ACCEPTANCE OF PRIVATE PHYSICIANS' INTERPRETATION OF X-RAY FILMS OF SCHOOL PERSONNEL

During the past two or three months several inquiries have come to the Department of Public Health concerning whether a private radiologist's interpretation of a chest x-ray film is acceptable as a basis for a physician's certificate to a school superintendent or principal that a given school employee is not suffering from tuberculosis in a communicable form.

In this connection the Department has ruled that it will accept a private radiologist's x-ray film and his interpretation for purposes of certification. The legislative act concerning this matter provides that in questionable cases the film shall be submitted for review to the Department of Public Health or to the county or municipal tuberculosis sanatorium and that upon request of the Department the sanatorium shall make supplementary x-ray films and such laboratory and other examinations as are indicated to determine the communicability of a given lesion. The act further sets up a board of appeal of three physicians to whom cases in which the question of communicability of tuberculosis arises may be referred for final decision.

Questions have also been raised concerning the requirement of the act that the required physician's report be based on an x-ray film taken not more than ninety days prior to certification. In this connection it is clear that the intent of the act is to limit the period of certification to ninety days after the roentgenogram is taken. This interval has no reference to the time between certification and the employment of a specific person.

Alton S. Pope, M.D., *Director*
Division of Tuberculosis and Sanatoria

PUBLIC HEALTH SERVICE SUGGESTS FLUORIDATION

Experimental fluoridation of public water supplies has been in operation in several states for a sufficiently long period for the early effects of this process on the caries susceptibility of the deciduous teeth and some permanent teeth of children to be observed.

The observations on caries prevalence in children exposed to artificial fluoridation as compared with control groups exposed to both relatively fluorine-free potable waters and naturally occurring optimal fluoride concentration have prompted the

following statement by the United States Public Health Service:

Preliminary data suggest a lowered amount of dental decay following fluoridation of the public water supply. Although evidence is rapidly accumulating, the control studies now being carried on should be continued and others initiated as may be necessary.

In order to utilize this preventive at the earliest possible moment, formulation of plans for fluoridation of public water supplies as a procedure for the partial control of dental caries may be encouraged subject to the approval of the State and local health authorities and the dental and medical professions.

WILLIAM D. WELLOCK, D.M.D.
Division of Dental Health

GEORGIA ACCEPTS MASSACHUSETTS MARRIAGE CERTIFICATE

The Georgia Department of Public Health has informed the Department that as a result of their recently amended premarital-examination law the marriage registrars have been authorized to accept the Massachusetts premarital-examination certificate when it is properly completed by a Massachusetts physician.

(This information should be added to the list published on page 195 in the issue of February 1, 1951.)

NICHOLAS J. FIUMARA, M.D.
Division of Venereal Diseases

CORRESPONDENCE

EXPRESSION OF OPINION

To the Editor: May I congratulate you on the editorial in the *Journal* of March 8 on "Overplaying the Hand."

This editorial points up the objection that is so distressing to most of us who want the American Medical Association to continue its many good influences and who do not want to see medicine fall into the control of the Federal government but who at the same time deplore the low standards set by the present advertising campaign. At the present time there is hardly any way that one can exercise effective protest against the Whitaker-Baxter Program except by withdrawing from the American Medical Association entirely. It is my hope that well expressed protests like that in your editorial will bring the present leadership of the Association back to a reasonable attitude that will satisfy most physicians. I do not even think or hope that we can get unanimity of opinion among the 200,000 physicians in the United States. It would not even be desirable. I do believe that we have a right to have our varying opinions expressed in the various publications of the American Medical Association. It will not weaken the medical profession in the eyes of the American public to know that we have many shades of opinions on social and political topics. It will on the contrary strengthen the medical profession to have this fact known.

DANA L. FARNSWORTH, M.D.
Belmont, Massachusetts

SALT OF THE SEA

To the Editor: The recent article by Doctors Nizel and Harris on the caries-producing effect of similar foods grown in different soil areas is interesting and timely. For many years our agricultural chemists and agronomists have been stressing the fact that our soil is steadily being depleted of its trace elements by the combination of excessive cropping and leaching through broken sod. This loss of minerals from our soil is now being reflected in trace-element-deficient food on our dinner tables.

Experiments conducted by the agriculture departments of the Federal government and many of our states have led to the prescription of mineral supplements to be added to the soil with the usual P.N.P. fertilizers and lime. Stress, however, has been on the replacement of those elements that are essential to plant growth, and no effort has been made to replace trace elements, which although not essential to plant growth are essential to human health.

In the past the trace-element deficiencies in our food were not too important because the missing elements were available, for the most part, in our table salt. In recent years, however, the salt producers have refined their table salt almost to the point of chemical purity in their effort to market a product that will not "cake" in damp weather. In this process much of the trace-element material essential to health is lost. It appears that we still have not profited by past experience with polished rice.

Recent studies in electrolyte balance have called attention to the striking similarity, both quantitative and qualitative, of the electrolyte content of sea water to that of our total body fluids. It is obvious from this that unrefined sea salt is an excellent source of trace elements, both those that are now recognized as important and others that are not yet known to be essential but may be found essential to health in the future. In the light of recent discoveries about cobalt it would be arrogant for any of us to deny the possibility of some essential function for even gold in our complex metabolism — and sea water contains this precious metal.

At the risk of being considered a food faddist (hence queer), I strongly advocate the use of sea salt in the preparation and seasoning of our food. It is available in shops catering to the special-diet trade. It does not shake well and it "cakes" even in dry weather, but these inconveniences are minor in view of its value in supplying us with the trace elements now lacking in our diet.

S. HORCHSTETTER, M.D.
Rutland Heights, Massachusetts

THE ANESTHESIA NURSE

To the Editor: Briefly reviewing the history of the nurse in the surgical and obstetrical departments of the hospital, it is found that the nurse has been an assistant to the physician in the operating room and the case room for many years. Until a decade ago the nurse was even the surgeon's first assistant at his private operations. This practice was discontinued when it was deemed necessary to employ a surgeon as the assistant for the greater safety of the patient. The employment of the obstetrical nurse as assistant to the obstetrician in the Lying-In Hospital followed the time when the midwife was no longer generally employed and the specialist in obstetrics had become accepted in this special field of medicine.

Ether, almost the sole anesthetic agent from the time of its first public demonstration in 1846 in Boston until the early 1900's, was administered by comparatively few physicians who recognized that physiologic problems were involved. At this time, when relatively few scientific advances had been made in the field of anesthesia, the duty of etherizing patients was relegated for the most part to the nurse in the surgical hospital.

Despite the fact that many advances had been developed by physicians interested in the scientific aspects of anesthesiology, by 1930 28,000 nurses and only 500 physicians were administering anesthetics in the United States. Thereby a vicious cycle was created. The employment of the nurse deterred the physician from entering this specialty, and as much more surgery was being performed a larger number of physician-anesthetists was sorely needed for intelligent administration of the required anesthesia. Beecher* says: "Until recent years, almost the entire specialty in this country has rested in the hands of the nurses." He further states: " . . . but so far as I know no nurse has ever made a single contribution to anesthesia." In England only registered physicians

*Beecher, H. K. Specialty of anesthesia and its application in Harvard University-Massachusetts General Hospital department. *Ann. Surg.* 126: 486-499, 1947.

have ever been allowed to administer anesthetics to the patient, and for the past eight years it has been unlawful for any person except a licensed physician to practice anesthesia in Canada.

At the present time, there are over 4000 physicians in the United States whose practice is limited to anesthesiology. This is a result of the many advances made by physicians interested in this branch of medicine. Of first importance has been the placing of anesthesia on a scientific basis by the clinical application of all basic sciences of medicine, particularly physiology and pharmacology. The increase in the number of physicians entering the specialty has been primarily due to the organization of courses and departments in anesthesiology at the leading medical schools and teaching hospitals in the past twenty-five years. Raising of the standards of hospitals by the American College of Surgeons, requiring physicians to supervise departments of anesthesiology, led more physicians to enter the field and, together with the recognition of anesthesiology by the American Board of Specialties, has elevated this field of medicine to an equal rank with all other specialties.

Today, the anesthesiologist has too many things to do in the performance of his task to provide the utmost safety for the patient without sufficient assistance. Among these are many complicated technics and functions to carry out in the administration of the most lethal drugs used in medicine for the relief of pain and preservation of the patient's physiology. For example, there is the re-examination of the patient on arrival at the operating room; positioning of the patient; administration of not only the anesthetics but the supplementary drugs, fluids and blood transfusions; minute-by-minute evaluation of the physical signs of the drugs used for anesthesia; continual checking of the clinical course to prevent overdose of the drugs, development of hypoxia and other complications. During this critical period in the course of anesthesia, for these and many other reasons, the anesthesiologist is in desperate need of a trained assistant. In this respect, there is a great need of the nurse who is interested in anesthesia. At the present stage of evolution of this specialty, and in view of the scarcity of physicians, training the nurse to assist the anesthesiologist is a real step in the direction of better preparation of the patient for anesthesia and better end results in surgery.

The Department of Anesthesiology at the Boston City Hospital is offering a new course for the training of the nurse as assistant to the anesthesiologist. The participant in this course will be designated as the anesthesia nurse. The following is an outline of the plan whereby the nurse may receive this special training in the field of anesthesiology, just as the surgical nurse or obstetrical nurse receives her training under the supervision of the respective departments.

The anesthesia nurse will receive training in the fundamentals of the theory and practice of anesthesiology. The care and preparation of supplies and equipment will be assigned to her. This will include all drugs, anesthetics and gases; apparatus for inhalation and endotracheal technics and spinal, regional and intravenous anesthesia and intravenous and inhalation therapy. She will also be trained in the modern methods of resuscitation of the patient.

The duties of the anesthesia nurse may be briefly summarized. In the preanesthetic period she will aid in the preparation of the patient and anesthetic equipment in the operating room and aid the anesthesiologist during induction. During the maintenance period, the anesthesia nurse will be in constant attendance on the anesthesiologist to assist in the care of the patient in emergencies and to secure anesthetics, therapeutic drugs and prophylactic fluids. In the postoperative period she will aid the anesthesiologist in resuscitation and in meeting the emergency needs of the patient. She will chaperone the patient from the operating room to the postoperative recovery room or to his bed; institute the immediate postoperative orders; attend the patient in distress in the absence of the physician; perform aspiration, administer inhalation and intravenous therapy and, if need be, apply artificial respiration for resuscitation. Some of these nurses trained in anesthesiology will be available for the supervision of the postoperative recovery room.

In summary, a rough plan for the training of the anesthesia nurse has been offered, whereby many ideals in anesthesiology may be achieved. The objectives are: to create trained assistants in anesthesiology to aid the departments of anesthesia in all hospitals; to give the patient better professional care; and to save valuable time for the surgeon and add to his efficiency, at the same time augmenting the efficiency of the anesthesiologist. Most important is the fact that this evolution of the nurse in anesthesiology will greatly benefit the patient. The anesthesia nurse will then occupy a definite and permanent place in the field of anesthesiology, beside the surgical and obstetrical nurse.

SIDNEY C. WIGGIN, M.D., *Director*
FRANCIS X. MACK, M.D., *Assistant Director*
Department of Anesthesiology, Boston City Hospital
Boston, Massachusetts

BOOK REVIEWS

Supervoltage Roentgentherapy. By Franz Buschke, M.D., Simeon T. Cantril, M.D., and Herbert M. Parker, M.Sc. 8°, cloth, 297 pp., with 150 illustrations and 19 tables. Springfield, Illinois: Charles C Thomas, 1950. $10.50.

In 1945 Charles C Thomas reprinted a thin book of 137 pages by Phillips and Innes on the subject "Super-Voltage X-ray Therapy." This was based on experience in the use of the 1000-kv. generator at St. Bartholomew's Hospital, London, between the years 1937 and 1942.

In 1950 the same publishers brought out this new book reporting experience in the use of an 800-kv. P. unit at the Swedish Hospital in Seattle, Washington, during the years 1932 through 1945.

The first chapter consists of a brief description of the apparatus used at the Swedish Hospital, which in view of current trends in engineering of supervoltage equipment is of historical interest only, and a review of the physical factors on which the advantages of supervoltage therapy are based. These are clearly and honestly presented, and though the physical data do not extend into the range of present supervoltage radiation, or into the range of what may be called "supervoltage" radiation in the future, the fundamental tenets that give supervoltage radiation an advantage are valid. These advantages are increased depth dose, skin tolerance, reduced integral dose with respect to tumor dose, lessened differential absorption in tissues of varying densities and the like.

Nine chapters follow, in which the authors review, system by system, their experience in the treatment of malignant neoplasms by supervoltage radiation. Their results and the means by which they were obtained are presented by useful charts, good teaching cases and many illustrations, 20 of which are in color. Perhaps more important, however, from the standpoint of the general radiologist are the statements of the authors' general concepts of neoplastic disease and its treatment by radiotherapy. The points of view presented are as applicable to roentgen-ray therapy in the ordinary voltage brackets as they are in the supervoltage ranges. The advantages afforded by supervoltage radiation in the treatment of various lesions are, however, brought out.

By and large, the authors have given what appears to be an honest and reasonable point of view concerning the use of supervoltage x-rays in the management of malignant neoplasms, and in addition have included many general precepts regarding the recognition, classification and management of cancer.

Regional Dermatologic Diagnosis: A Practical System of Dermatology for the Non-Specialist. By Ervin Epstein, M.D. 8°, cloth, 328 pp., with 148 illustrations. Philadelphia: Lea and Febiger, 1950. $6.00.

When the general practitioner fails to recognize the diagnosis of a patient presenting a skin eruption, it is difficult for him to decide what disease to study in his textbook of dermatology. He might decide that it is one of several diseases, among which is the very common one of scabies. He is therefore obliged to read several chapters, and by the time he has finished these he is apt to be confused.

Epstein, by his topical and regional description of the various skin diseases, has removed this confusion, and in one chapter has grouped all the diseases affecting any one part predominantly. Since many cutaneous diseases do affect one area more than another, the practicing physician should find this book very useful.

It has numerous excellent illustrations. Charts showing the differential diagnoses of the eruptions on various areas

reduce one's reading to a minimum and present a clear-cut picture. His treatments are brief and extremely useful. There is little to criticize. Perhaps the main objection from anyone reviewing the book or attempting to read it from cover to cover would be to the constant repetition. However, repetition is always valuable to the student. The greatest criticism that can be made concerns the treatment recommended for nevi. His recommended therapy of elevated lesions consists of shaving the nodule off at the level of the skin, this to be followed by an application of trichloracetic acid, which is neutralized by alcohol. Because of the great possibility of error in the diagnosis of these lesions it is thought that this recommendation is dangerous. Surgical excision for biopsy is preferable. The reviewer does not hesitate to recommend this book to the general practitioner as a useful addition to his library.

J. G. Downing, M.D.

Practical Gynecology. By Walter J. Reich, M.D., and Mitchell J. Nechtow, M.D. 8°, cloth, 449 pp., with 187 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $10.00.

This book is primarily a manual of office gynecology: it represents the authors' own practical technics and their teaching at the Cook County Hospital in Chicago. It is complete, compendious, well written and well arranged, with 187 admirable illustrations, of which 55 are in color. Among the most interesting, unusual and valuable portions are the introductory chapter on the psychosomatics of gynecology and those on reproductive endocrinology. It should take its place among the standard texts of clinical office practice.

Robert M. Green, M.D.

Bone and Joint Diseases: Pathology correlated with roentgenological and clinical features. By J. Vernon Luck, M.D. 4°, cloth, 614 pp., with 454 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $16.50.

There has long been a need for a book of this type, which combines a description of the pathologic changes with the findings in x-ray films and clinical examination. The author is to be congratulated on the thoroughness of his pathological studies. The format of the book is excellent. It is profusely illustrated with photographs of good quality. The style is clear, concise and easily readable. The references are up-to-date and well chosen. One is pleased to see an arrangement of diseases of the locomotor apparatus according to their chief pathologic features. Whether or not avascular osseous necrosis will be the ultimate nosologic classification for a large group of entities that now appear under the name of their discoverer, the author has gone a long way toward bringing order out of chaos. It is most gratifying to see how far we have come in the understanding of the physical and biochemical processes of those diseases that fall in the domain of orthopedic surgery. However, a book of this type leaves us at the threshold of many unknowns. The entire book is good, but the author has not succeeded as well in the clinical correlation as he has in the roentgenologic and pathologic descriptions. Perhaps this is too much to ask. Suffice it to say that the author has performed a meritorious task in bringing us a fairly complete pathological text of diseases of the bones and joints. This is a book that should be studied carefully by all orthopedic surgeons.

John G. Kuhns, M.D

Surgery of Cataract. By Daniel B. Kirby, A.M., M.D., LL.D. 4°, cloth, 695 pp., with 339 illustrations. Philadelphia: J. B. Lippincott Company, 1950. $30.00.

In this 695-page book, replete with illustrations (339) and colored plates (21), Dr. Kirby gives to the world of ophthalmology a deluxe monograph. Photographs of many eminent ophthalmologists are included. The author quotes freely from authorities to portray both sides of controversial points.

The reviewer is disappointed to find the author clinging to the designation "cataract" for the dozens of lens blemishes, congenital and otherwise, that are seldom progressive, and that seldom interfere with useful vision. A treatise of the scope of this book should have the courage to champion replacement of an outmoded nomenclature with one built on the more exact foundations of slit-lamp microscopy.

The subject of diabetic cataract is poorly covered. The author admits that the only distinctive cataract in diabetics is to be found in the "snowflake" cataract of poorly treated juvenile diabetics. Under the term "diabetic cataract" he includes all types of senile degeneration of the crystalline lens. The fact is that other workers have found, in the examination of large series of patients after midlife, that the incidence of senile imperfections in the lens is practically the same in diabetics as in nondiabetics of corresponding age.

J. Herbert Waite, M.D.

Immortal Magyar: Semmelweis, Conqueror of Childbed Fever. By Frank G. Slaughter, M.D. 8°, cloth, 211 pp., with 4 illustrations and frontispiece. New York: Henry Schuman, 1950. $3.50.

This popular story of the life of Semmelweis is written in narrative form and tells of his discovery of the source of infection of the dread puerperal fever. In 1861 he published his monumental *Die Aetiologie, der Begriff und die Prophylaxis des Kindbettfiebers.* The second part of his book was devoted to the controversial letters written to him, and also published, by famous obstetricians. This book was almost universally ignored and Semmelweis rushed into print with his two *Offene Briefe,* published in Pest in 1861 and 1862 and addressed to J. Spaeth and F. W. Scanzoni and other professors of obstetrics.

Oliver Wendell Holmes, working independently in Boston, published his discovery of the causation of puerperal fever in 1843 in the *New England Quarterly Journal of Medicine and Surgery.* Like Semmelweis, he was attacked and ridiculed by eminent obstetricians of the United States. In 1855 his paper was republished under the title "Puerperal Fever as a Private Pestilence."

In this volume he devoted twenty-four pages to answering his critics, and reprinted his original "Contagiousness of Puerperal Fever." Dr. Holmes evidently intended publishing a third edition, as the Boston Medical Library has a copy of the second edition containing many manuscript notes, corrections and changes. For some unknown reason this contemplated edition was not published.

The Boston Medical Library has fine copies of all the items mentioned in this review.

James F. Ballard

Cytology of the Human Vagina. By Ines L. D. de Allende, M.D., and Oscar Orias, M.D. With a foreword by Bernardo A. Houssay, M.D., translated from the Spanish by George W. Corner, M.D. 8°, cloth, 286 pp., with 75 illustrations. New York: Paul B. Hoeber, Inc., 1950. $7.50.

It was in 1892 that Lataste first began his study of gynecologic endocrinology by means of stained vaginal smears, revived in 1917 by Stockard and Papanicolaou, and continued by Long and Evans in 1922. Since that time our knowledge of the entire subject has been enormously advanced, and cytologic examination of the vaginal contents has become the established method of investigating the trophic and cyclic functions of the female sex hormones in health and in disease.

The present monograph embodies the research studies in this field carried out by its authors during the past five years at the Institute of Physiology of the University of Cordoba, Argentina, employing the Shorr trichrome stain. It aims to demonstrate the easy and reliable application of this stain to vaginal smears; to describe the normal human vaginal cycle and establish a basal pattern with which to compare abnormal cases; to describe in detail the typical pictures of the functional anomalies of the female sex cycle; and to furnish a guide to those who wish to carry on further study of human vaginal smears.

This immensely valuable work is illustrated with 75 figures, 22 of them in colors, and concludes with a bibliography of 140 titles. The foreword is by the distinguished Argentine endocrinologist and physiologist, Dr. Houssay; the admirable English translation from the Spanish original has been made by Dr. Corner, director of the Department of Embryology of the Carnegie Institution.

Robert M. Green, M.D.

Understanding Natural Childbirth: A Book for the Expectant Mother. By Herbert Thoms, M.D. With the collaboration of Laurence G. Roth, M.D., and with a picture story by David Linton. 4°, cloth, 112 pp., with illustrations. New York: McGraw-Hill Book Company, Inc., 1950. $3.50.

This valuable volume, deriving fundamentally from the idea advanced by Dr. Grantly Read in his "Childbirth without

Fear," is a popular presentation, for prospective mothers, of the work done in recent years by the authors at the Grace–New Haven Community Hospital under the auspices of the Department of Obstetrics and Gynecology of the Yale University School of Medicine.

In concept, the theory of "natural childbirth" dates back to the practice of certain sagacious obstetricians at the Harvard Medical School and the Boston Lying-in Hospital fifty years ago. The present authors, however, have amplified it by the important details of prenatal training, intelligent maternal co-operation during labor and the admirable practice of "rooming-in." All these phases are abundantly illustrated by numerous photographs, many of which originally appeared in *Life* magazine. There is also an excellent series of six sculptures of the birth process from the "Birth Atlas," published by the Maternity Centre Association.

This is one of the best of the many popular texts published in recent years for prospective parents.

ROBERT M. GREEN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Genealogy of Gynaecology: History of the development of gynaecology throughout the ages. 2000 B.C.–1800 A.D., with excerpts from the many authors who have contributed to the various phases of the subject. By James V. Ricci, M.D., clinical professor of gynecology and obstetrics, New York Medical College, director of gynecology, City Hospital, New York, attending gynecologist and obstetrician, Flower and Fifth Avenue Hospitals, consultant in gynecology and obstetrics, Beekman–Downtown Hospital, and consultant in gynecology and obstetrics, Columbus Hospital. Second edition. 4°, cloth, 494 pp. Philadelphia: Blakiston Company, 1950. $8.50.

The first edition of this historical book was published in 1943. In the present edition the work has been enlarged and completely revised by Dr. Curt Proskauer. In addition to material on the history of gynecology and obstetrics, there is of necessity much information on the history of medicine in general. A smaller type and non-glare paper, making for easier reading, is used in the second edition. The volume is lighter in weight and easier to handle. There is an index of personal names but not of subjects. Otherwise, the book is well published and should be in all medical-history collections.

Medical Diagnosis: Applied physical diagnosis. Edited by Roscoe L. Pullen, M.D., professor of graduate medicine, director of the Division of Graduate Medicine and vice-dean, Tulane University of Louisiana School of Medicine, senior visiting physician, Charity Hospital of Louisiana at New Orleans, consultant in medicine, Veterans Administration Hospital, New Orleans, Louisiana, and consultant to the Surgeon General, Department of the Army, Washington, D. C. Second edition. 8°, cloth, 1119 pp., with 601 illustrations. Philadelphia: W. B. Saunders Company, 1950. $12.50.

This new edition of a book first published in 1944 has been revised and brought up to date for the needs of the general practitioner. The sections on the examinations of the eye and the abdomen and on electrocardiographic interpretation have been completely rewritten. Chapters have been added on bedside diagnosis of blood diseases, medical diagnosis in the aged and the physical examination of the psychiatric patient. The volume is the joint work of 23 contributors. There is a large index, and the publishing is good. The book should be in the reference collections of medical libraries and should prove useful to practicing physicians.

A Textbook of Gynecology. By Arthur H. Curtis, M.D., and John W. Huffman, M.D., associate professor of obstetrics and gynecology, Northwestern University Medical School, and attending gynecologist, Passavant Memorial Hospital, Chicago. Sixth edition. 8°, cloth, 799 pp., with 466 illustrations. Philadelphia: W. B. Saunders Company, 1950. $10.00.

In this new edition, a standard book, last published in 1946, has been thoroughly revised and brought up to date. The chapters on embryology and on urinary-tract problems in gynecology have been extensively revised. New material includes data on the sarcomatous growth of the cervical stroma, the paraurethral ducts, and mesonephric remnants in the cervix. Numerous illustrations have been added. The illustrations are excellent. There is a good index and the publishing is good. The book should be in all medical libraries as a standard reference work and available to all physicians interested in the subject.

Primary Carcinoma of the Vagina. By Robert G. Livingstone, M.D. 8°, cloth, 73 pp., with 2 figures and 8 tables. Springfield, Illinois: Charles C Thomas, 1950. $2.00.

This study of the rare disease of primary carcinoma of the vagina is based on a consecutive and unselected series of 110 patients admitted to the Memorial Hospital during the period December, 1925, to January, 1946. All the aspects of the disease are discussed, including etiology and symptomatology, diagnosis, treatment, end results and prognosis. A five-year cure rate of 10.5 per cent has been determined for 76 of the 110 patients in the series of cases. There is a comparatively extensive bibliography but no index. The printing was done by lithography satisfactorily, but it is not as easy on the eyes as printing from type.

Oral and Facial Cancer. By Bernard G. Sarnat, M.D., professor and head of the department of Oral and Maxillofacial Surgery, College of Dentistry, and clinical assistant professor of surgery, College of Medicine and Research and Educational Hospital, University of Illinois, Chicago; and Isaac Schour, D.D.S., Ph.D., Sc.D., co-ordinator of cancer instruction, professor and head of the Department of Histology and associate dean in charge of postgraduate studies, University of Illinois College of Dentistry, Chicago. With a foreword by Andrew C. Ivy, Ph.D., M.D., D.Sc., vice-president in charge of Chicago Professional Colleges, University of Illinois, and executive director of the National Advisory Cancer Council. 8°, cloth, 300 pp., with 118 illustrations. Chicago: Year Book Publishers, Incorporated, 1950. $6.00.

This small book is written for teaching purposes and also to serve the general practitioner as a manual for general reference. The main objective is the early recognition and treatment of cancer of the face and mouth. The combination of a physician and a dentist is ideal in the writing of this type of book. The text is divided into three main parts: the cancer problem, discussing the public-health aspects and the present status of cancer research; clinical aspects of oral and facial cancer, including carcinoma of the soft tissues, face and mouth, and cancer of the jaws, mandible and maxilla; and a discussion of the control of oral and facial cancer and the place in the program of the patient, general practitioner and specialist, including the physician, dentist and surgeon. Selected case histories to illustrate the various types of tumors have been included in the text. The material has been well organized, and the text well written and illustrated. The words cancer and carcinoma have been used interchangeably, which might lead to some confusion to the uninformed person. It would have been better to adhere to one form for the purpose of lucidity. A short bibliography and a good index conclude the volume, which is well published. The book should be in all collections on cancer and available to all physicians and dentists.

Human Milk: Wartime studies of certain vitamins and other constituents. By S. K. Kon and E. H. Mawson. 8°, paper, 188 pp., with 19 figures and 95 tables. London: His Majesty's Stationery Office, 1950. 4s. (Medical Research Council Special Report Series, No. 269.)

In this monograph the authors discuss the constituents of human milk, and the relation between the constituents studied and nutritional standards.

Researches on the Measurement of Human Performance. By N. H. Mackworth. 8°, paper, 156 pp., with 58 illustrations. London: His Majesty's Stationery Office, 1950. 4s. (Medical Research Council Special Report Series, No. 268.)

This study in the field of experimental psychology is divided into two main parts. The first is devoted to vigilance tests, including visual and auditory tests. The second dis-

cusses environmental stress tests, including tests for the effects of nonlethal war gases and for those of high atmospheric temperatures.

Researches on the Radiotherapy of Oral Cancer. By Constance A. P. Wood and J. W. Boag (with P. Howard-Flanders, A. Glückman, L. H. Gray and F. G. Spear). 8°, paper, 148 pp., with 76 figures and 32 tables. London: His Majesty's Stationery Office. 12s. 6d. (Medical Research Council Special Report Series No. 267.)

This monograph is divided into four main parts: an experimental comparison between gamma rays and x-rays; histologic investigations; statistical analysis of the history, physical signs and response to treatment; and further research in radiotherapy. There are two appendixes. One discusses determination by the method of maximum likelihood of the proportion cured and the other determination by an actuarial method of the proportion cured. This comprehensive study should be in all collections on diseases of the mouth, cancer and radiotherapy.

A Study of Diphtheria in Two Areas of Great Britain: With special reference to the antitoxin concentration of the serum of inoculated and noninoculated patients and other persons; and the relation of this to the incidence, type, and severity of the disease. By Percival Hartley, Kt., C.B.E., M.C., D.Sc., F.R.S., and others. 8°, paper, 162 pp., with 9 figures and 81 tables. London: His Majesty's Stationery Office, 1950. 4s. (Medical Research Council Special Report Series, No. 272.)

Mass immunization against diphtheria was initiated in England in 1941, and has resulted in a rapid fall in the incidence and mortality of the disease. The epidemics at Tyneside and at Dundee, in which 30 to 50 per cent of the cases occurred in previously inoculated persons, provided an excellent opportunity to study the end results of the mass inoculation. The authors have made a comprehensive survey of the epidemic in the two towns, with a view to improving diphtheria prophylaxis. The monograph should be in all collections on diphtheria. The special report series of the Medical Research Council are outstanding in their excellence, and the complete series should be available in all large communities.

A Primer for Diabetic Patients: An outline of treatment for diabetes with diet and insulin including directions and charts for the use of physicians in planning diet prescriptions. By Russell M. Wilder, M.D., Ph.D., professor and chief of the Department of Medicine, Mayo Foundation, University of Minnesota, and senior consultant in the division of medicine, Mayo Clinic. Ninth edition. 12°, cloth, 200 pp., with 8 illustrations. Philadelphia: W. B. Saunders Company, 1950. $2.25.

This popular manual from the Mayo Clinic, last published in 1946, has been revised to conform to certain changes in procedure adopted by the Clinic. The tendency has been to be "somewhat more liberal in dietary recommendations for patients using insulin, and when insulin is used, to advise somewhat less rigidity than formerly in the control of glycosuria." The small volume is well published and sold at a low price. It is suitable for public libraries and for lay collections in medical libraries.

Aetios of Amida: The gynaecology and obstetrics of the VIth century, A.D. Translated from the Latin edition of Cornarius, 1524, and fully annotated by James V. Ricci, M.D., clinical professor of gynecology and obstetrics, New York Medical College, director of gynecology, City Hospital, New York, attending gynecologist and obstetrician, Flower and Fifth Avenue Hospitals, consultant in gynecology and obstetrics, Beekman-Downtown Hospital, and consultant in gynecology and obstetrics, Columbus Hospital. 8°, cloth, 215 pp. Philadelphia: Blakiston Company, 1950. $7.00.

This classic contribution of the sixth century is now made available to scholars. It comprises the sixteenth book of the *Tetrabiblon* of Aetios. Preceding the text there is a short historical sketch. The volume concludes with forty-seven pages of notes on the text and a list of vegetable, animal and mineral substances used in the treatment of female diseases by Aetios. The book is well published and should be in all medical historical collections. A copy of the 1534 edition is in the Boston Medical Library.

Annual Review of Medicine. Windsor C. Cutting, editor, Stanford University School of Medicine, and Henry W. Newman, associate editor, Stanford University School of Medicine. Vol. I. 8°, cloth, 484 pp. Stanford, California: Annual Reviews, Incorporated, 1950. $6.00.

This first volume of a new series of progress reports covers the field of medicine in a broad manner, including obstetrics, psychiatry, some surgical subjects, anesthesia, radiology and ear, nose and throat, in addition to the regular subjects in the field of internal medicine. Twenty-one specialists review the recent literature on their particular subjects. Each article is documented with a list of references cited in the text. In addition, a bibliography of twenty-two pages of reviews published in medical periodicals between July, 1948, and November, 1949, is appended to the text. This list is arranged by subjects. There are indexes of authors and subjects, and the publishing is excellent. The price is low. The volume should prove valuable to the practicing physician.

Amusing Quotations for Doctors and Patients. Edited by Noah D. Fabricant, M.D. 12°, cloth, 149 pp. New York: Grune and Stratton, 1950. $3.00.

The quotations in this small book, all of medical interest, have been selected from a large number of authors, from Homer to Oliver Wendell Holmes. The arrangement is alphabetical by subjects.

NOTICES

U. S. NAVAL RESERVE VOLUNTEER MEDICAL UNIT NO. 1-1

Two meetings of Volunteer Medical Unit No. 1-1, U. S. Naval Reserve, will be held in May at Children's Hospital, 300 Longwood Avenue, Boston. Both meetings will begin at 7:30 p.m. On May 9 Dr. Quentin Geiman, associate professor of tropical public health, Harvard Medical School, will speak on "Recent Advances in Malaria, Amebic Dysentery and Yaws." On May 23 Dr. Kenneth J. Welch, assistant in surgery, Harvard Medical School and Tufts College School of Medicine, will discuss "Fluid and Electrolyte Problems in Atom Bomb Casualties."

Physicians and medical students are invited to attend.

SPRINGFIELD ACADEMY OF MEDICINE

A meeting of the Springfield Academy of Medicine will be held in the Woman's Club Building, 43 Spring Street, on May 8 at 8:30 p.m. Dr. Vernon Knight, member of the faculty of Cornell University, will speak on the subject "Modern Treatment with Antibiotics."

MASSACHUSETTS TRUDEAU SOCIETY

The spring meeting of the Massachusetts Trudeau Society will be held at Worcester County Sanatorium, Worcester, on Tuesday, May 8, at 7:45 p.m. Drs. Raymond H. Goodale, pathologist, Worcester Hahnemann Hospital, Paul F. Ware, thoracic surgeon, St. Vincent Hospital, and consulting thoracic surgeon, Memorial Hospital, and William J. Elliott, roentgenologist, Memorial Hospital, will discuss the subject "The Problem of Sarcoid." There will be an election of officers.

All interested persons are invited to attend.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the Boston City Hospital will present a lecture on May 15, at 7:00 p.m., in the Cheever Amphitheater of the Dowling Building, as a part of the association's Tuesday Evening Lecture Series. Dr. Louis K. Diamond, of the Children's Medical Center, will speak on "The Clinical Aspects of Rh Sensitization." Discussers will be Drs. William B. Castle and William C. Maloney.

All interested persons are invited to attend.

AMERICAN PROCTOLOGIC SOCIETY

The annual meeting of the American Proctologic Society will be held in Atlantic City, New Jersey, June 6-9. The Joseph Mathews Biennial Oration will be given by Dr. Frank C. Yeomans of New York City.

(Notices concluded on page xvii)